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A three-component synthesis of pyrido[2,3-*d*]pyrimidines

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Abstract—A new, high yield multicomponent reaction providing multifunctionalized pyrido[2,3-*d*]pyrimidines in a microwave-assisted one-pot cyclocondensation of α,β-unsaturated esters, amidine systems and malononitrile (or ethyl cyanoacetate) is described (the 'Victory' reaction).

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry. In times where a premium is put on speed, diversity, and efficiency in the drug discovery process, MCR strategies offer significant advantages over conventional linear-type syntheses.[1] MCRs leading to interesting heterocyclic scaffolds are particularly useful for the creation of diverse chemical libraries of 'drug-like' molecules for biological screening, since the combination of three or more small molecular weight building blocks in a single operation leads to high combinatorial efficacy. Herein we report a novel three-component synthesis of multifunctionalized pyrido[2,3-*d*]pyrimidine scaffolds employing one-pot condensations of α,β-unsaturated ester, amidine and malononitrile/cyanoacetate building blocks.

Pyrido[2,3-*d*]pyrimidines represent a heterocyclic ring system of considerable interest because of several biological activities associated with this scaffold. Some analogues have been found to act as antitumor agents inhibiting dihydrofolate reductases or tyrosine kinases,[2] while others are known antiviral agents.[3] Some time ago it was discovered by Victory and co-workers that this heterocyclic system can be prepared in a multistep sequence from 2-methoxy-6-oxo-1,4,5,6-tetrahydropyridin-3-carbonitrile intermediates **3** (Scheme 1), obtained by reaction of an α,β-unsaturated ester **1** and malononitrile **2** (G = CN) in NaOMe/MeOH.[4] The presence of a highly reactive methoxy group in pyridones **3** renders these heterocycles excellent substrates for further nucleophilic substitution or condensation pathways. Along those lines we have reported general protocols for the synthesis of bicyclic heterocycles such as pyrazolo[3,4-*b*]pyridines, 1,6-naphthyridines, and 4-amino-pyrido[2,3-*d*]pyrimidines **6** ($R^3 = NH_2$) by treatment of pyridones **3** with amidine systems **5** ($R^4 = NH_2$, H, Me, Ph).[4] More recently, we described an acyclic variation of the above protocol for the synthesis of pyridopyrimidines **6** ($R^3 = NH_2$) based on the isolation of the corresponding Michael adduct **4** (G = CN), that also allowed us to obtain 4-oxopyrido[2,3-*d*]pyrimidines **6** ($R^3 = OH$) by treatment of intermediates **4** (G = CO_2Me), synthesized by Michael addition of acrylate **1** and methyl cyanoacetate **2** (G = CO_2Me), with an amidine building block **5** (Scheme 1).[5,6] We now report that pyrido[2,3-*d*]pyrimidines **6** can be rapidly obtained in one-pot by a microwave-assisted cyclocondensation of α,β-unsaturated ester, amidine and malononitrile/cyanoacetate building blocks.

Our initial investigations involved treatment of a mixture of methyl acrylate (**1**, $R^1 = R^2 = H$), malononitrile (**2**, G = CN) and guanidine (**5**, $R^4 = NH_2$) in a variety of different solvents under microwave irradiation conditions. Preliminary experiments with conventional reflux conditions in e.g. MeOH or THF indicated that reflux for 24 h in an oil-bath were required in order for this multi-step sequence to be completed. Using sealed vessel microwave heating technology[7] at temperatures of 100–140°C full conversions were generally achieved within 10 minutes. A variety of different solvents such as MeOH, EtOH, THF and MeCN were utilized in our early optimization studies. In general the strongly microwave absorbing MeOH provided the highest yields of the desired products. After considerable exper-

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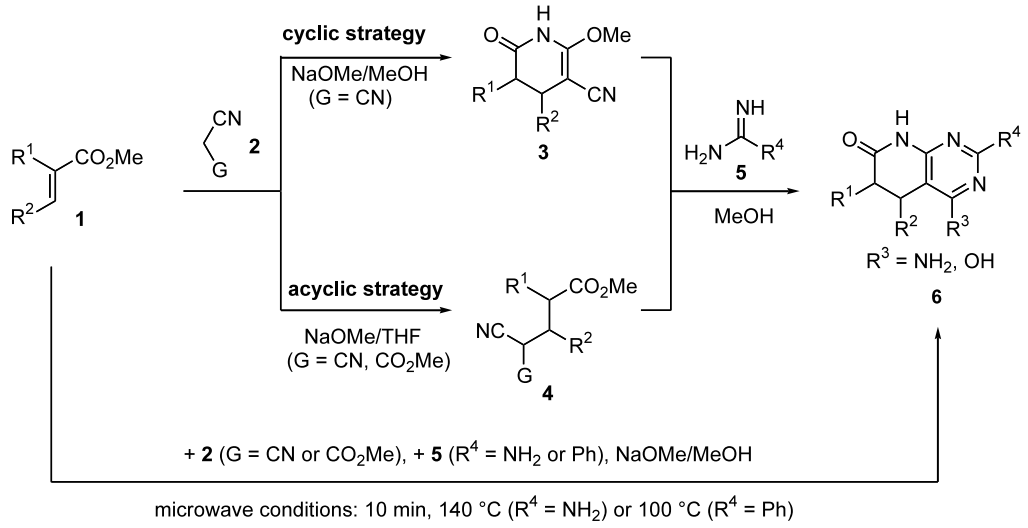

Scheme 1.

imentation with respect to the molar equivalents of reagents we arrived at conditions that utilized a 1:1.2:3 molar ratio of building blocks **1**/**2**/**5** and gave the most satisfactory results in terms of product yields and purity. The reaction was initially conducted in the absence of additional base. However, it was observed that, although guanidine is a base itself, a catalytic amount of a stronger base was necessary to obtain the desired product in high yield. Therefore, 5% of NaOMe was used to perform all cyclocondensation reactions.

Using those conditions a variety of different α,β-unsaturated esters **1** were employed for the synthesis of a small library of pyrido[2,3-*d*]pyrimidines (Table 1). In all cases using guanidine as amidine building block (**5**, $R^4 = NH_2$) the products simply crystallized in high yield after cooling of the reaction mixture to room temperature and were collected by filtration. The purity of all pyridopyrimidines was higher than 98% based on HPLC and ^1H NMR measurements. For those examples involving benzamidine (**5**, $R^4 = Ph$) purification by flash chromatography was required and the isolated yields were somewhat lower.

Table 1. Isolated yields of pyrido[2,3-*d*]pyrimidines **6** (Scheme 1)[a]

Entry	R^1	R^2	R^3	R^4	Yield (%)
1	H	H	NH_2	NH_2	>98
2	H	Me	NH_2	NH_2	>98
3	Me	H	NH_2	NH_2	>98
4	H	Ph	NH_2	NH_2	96
5	H	H	OH	NH_2	97
6	H	Me	OH	NH_2	>98
7	Me	H	OH	NH_2	87
8	H	Ph	OH	NH_2	88
9	H	H	NH_2	Ph	59
10	H	Me	OH	Ph	53

[a] Sealed vessel monomode microwave irradiation (10 min, 100–140°C), for details, see Ref. 8.

In conclusion, we have developed a new, rapid and simple multicomponent cyclocondensation protocol ('Victory' reaction) for the synthesis of biologically active pyridopyrimidines in high yields. The full exploration of this three-component process taking advantage of all four possible diversity points R^1–R^4 around the heterocyclic pyrido[2,3-*d*]pyrimidine core and further scaffold decoration are currently in progress and results will be reported in due course.

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8. All microwave experiments were performed using the Emrys Synthesizer (Personal Chemistry AB). **Typical procedure** (Entry 2, Table 1): Guanidine carbonate (180 mg, 3.0 mmol) was added to a fresh solution of NaOMe prepared by addition of 3.0 ml of MeOH to Na (70 mg, 3.05 mmol). The mixture was heated at reflux for 15 min. After cooling to rt the mixture was filtered to remove Na_2CO_3. The so prepared solution of guanidine in MeOH was placed in a microwave process vial containing a stir bar. After addition of methyl crotonate (100 mg, 1.0 mmol) and malononitrile (79 mg, 1.2 mmol), the vial was sealed and subjected to microwave irradiation for 10 min at 140°C. After gas jet cooling to rt (2 min) the formed precipitate was collected by filtration and washed thoroughly with water, EtOH and Et_2O providing an off-white powder (193 mg, 98%) that had >98% purity by HPLC and ^1H NMR. Recrystallization from AcOH produced the pyridopyrimidine **6** ($R^1=H$, $R^2=Me$, $R^3=R^4=NH_2$) in analytical purity. The spectral and analytical data were in agreement with authentic material.[4c,6]