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Alternative synthetic route to annulated diaminopyrimidines

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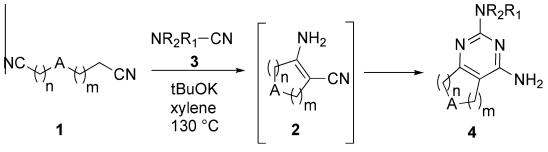
ABSTRACT

We report an alternative synthetic approach to annulated diaminopyrimidines based on a one-pot process, in which a Thorpe–Ziegler cyclization of a dinitrile is followed by in situ reaction with a cyanamide under highly concentrated and basic conditions. The total reaction can be carried out as fast as 30 min. The reaction mechanism is discussed. This one-pot synthetic route is universally applicable to a large variety of cyanamides and dinitriles, even natural products, to afford complex annulated diaminopyrimidines.

Annulated 2,4-diaminopyrimidine is a motif present in many synthetic molecules[1–5] and in a few natural products, mainly in the 7-deazaguanosine series, including, for example, archeosine[6] and queuine.[7] Diaminopyrimidines are prepared by multiple step synthesis[8,9] or, when possible, in a single step from a ketone and a dicyandiamide.[10–12] We wished to develop an alternative route to access rapidly and widely to fully substituted and annulated diaminopyrimidines, starting from dinitriles and cyanamide in basic and concentrated solution. Our sequence is based on the well-known Thorpe–Ziegler reaction,[13] which offers an easy access to enaminonitriles, recently discovered to react with non enolizable nitriles to offer the title compounds.[14] In addition, it was reported that cyanamides behave as nitriles and originate cycloaddition products with diynes under nickel or cobalt catalysis.[15,16] Furthermore, cyanamides, even complex ones, are readily available from the corresponding amines. Based on these findings, we have replaced nitriles with cyanamides to react with the enaminonitriles from the Thorpe–Ziegler reaction in order to form in a single step highly functionalized annulated diaminopyrimidines.

The one-pot reaction is depicted in Scheme 1. The cyclization of dinitrile **1** to afford β-cyanoenamine **2** as the intermediate is combined in situ, without isolation, with cyanamide **3** to give the desired product **4**. This method ensures access to a large panel of annulated diaminopyrimidine derivatives upon use of different dinitriles and cyanamides. In addition, the desired structures—annulated diaminopyrimidines—are obtained without the need to isolate and purify intermediate **2** and are recovered in high yield with few side products. The reaction is rapid, as fast as 30 min.



Scheme 1. One step synthesis of annulated diaminopyrimidines **4**. A is a hetero atom or a carbon atom, n and m correspond to the number of carbon atoms (1 or 2), when A is a cycle $m = 0$. *t*BuOK is potassium *tert*-butoxide.

The reaction reported in Scheme 1 was optimized. It tolerated a large excess of dinitrile **1** due to rapid formation of intermediate **2** that preferentially reacted with cyanamide **3** rather than with the starting dinitrile **1**. Thus, if the cyanamide is the most valuable compound in the sequence, it is best to use a large excess of dinitrile to bring the reaction to completion. Table 1 summarizes the results obtained by varying reaction time, base, and solvent. The optimization was carried on *para*-methoxybenzyl (PMB) protected dicyanoethylamine **1a** and morpholine-4-carbonitrile **3a** as model substrates of **1** and **3**, respectively.

The effect of the reagents' concentration was investigated. Dilution of the reaction gave lower yields of 6-(4-methoxybenzyl)-2-morpholino-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-amine **4a** (Table 1, compare entry I to entry III), therefore concentrated conditions must be chosen. A range of reaction times, from 30 min to 4 h, was tested. The reaction yield did not significantly change with

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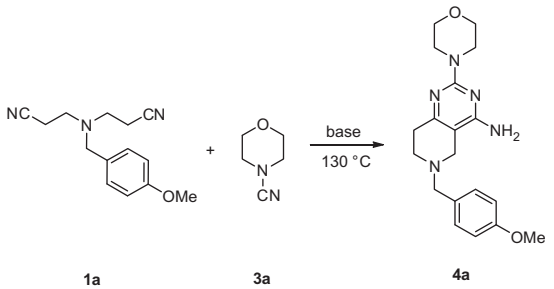
Table 1
Optimization of the reaction conditions on model substrates **1a** and **3a** (at 1.5 equiv and 1 equiv, respectively)



1a **3a** **4a**

Entry	Base	Time (h)	Solvent	Yield (%)
I	*t*BuOK	2	Xylene (0.054 M)	53
II	*t*BuOK	4	Xylene (1.8 M)	50
III	*t*BuOK	2	Xylene (1.8 M)	81
IV	*t*BuOK	1	Xylene (1.8 M)	78
V	*t*BuOK	0.5	Xylene (1.8 M)	81
VI	*t*BuOK	0.5	Xylene (1.8 M)	90[a]
VII	NaH	2	Xylene (1.8 M)	82
VIII	*t*BuOK	2	Pentanol (1.8 M)	0
IX	NaH	2	Pentanol (1.8 M)	0
X	*t*BuOK	2	DMF (1.8 M)	72
XI	NaH	2	DMF (1.8 M)	70

The yield was calculated compared to the starting cyanamide.
[a] This yield was obtained with 4 equiv of **1a**.

time between 2 h, 1 h, and 30 min (Table 1, entries II, III, IV, and V). Since reaction for 4 at high temperature led to the degradation of the reaction products, an average time of 2 h was chosen for the subsequent reactions.

Concerning the choice of the base, NaH and *t*BuOK gave similar yields when xylene or DMF was used as the solvent (Table 1, compare entries III to VI and X to XI). Noteworthy, the reaction tolerates DMF, thus allowing to run the method on compounds that are not soluble in xylene. Interestingly, when 1-pentanol was used as the solvent, the reaction stopped at intermediate **2** and no diaminopyrimidine could be detected whatever base was used (entries VIII and IX). Probably the pentanoate is not basic enough for the reaction to proceed further.

Under optimized conditions, a 90% yield of the annulated diaminopyrimidine **4a** was obtained upon use of a large excess (4 equiv) of starting material, PMB-protected 3,3′-azanediyldipropanenitrile **1a** (2.1 mmol), in 0.3 mL xylene at 130 °C for 30 min (entry VI), compared to 81% of yield for entry V of Table 1. Last, unprotected biscyanoethylamine **1g** was also engaged under these reaction conditions to yield 49% of the unprotected desired product N^2,N^2-dimethyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine-2,4-diamine **4g**, thus opening the way to further derivatives.

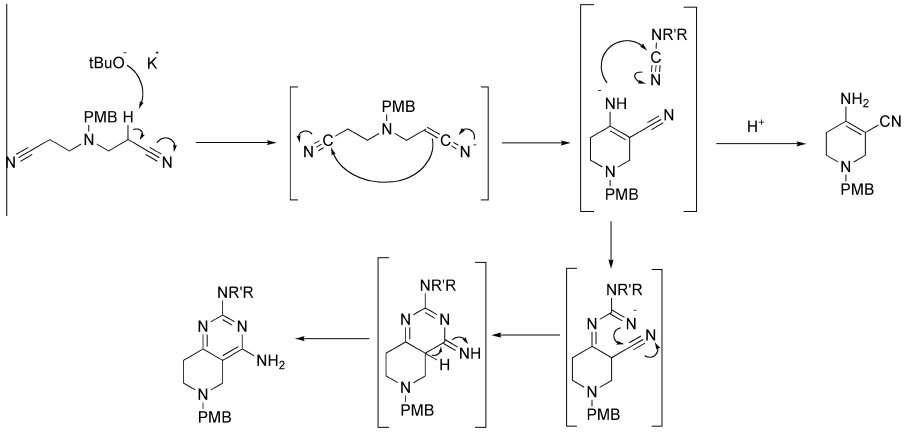
All results are in full agreement with the previous results published for the monoaminopyrimidine motif.[14]

Next we investigated the reaction mechanism. It involves two steps: an intramolecular cyclization, known as the Thorpe–Ziegler reaction, followed by the condensation of the intermediate enamine on the cyanamide to obtain the annulated diaminopyrimidines as depicted in Scheme 2. When intermediate **2a** was placed under the same reaction conditions with **3a**, the annulated diaminopyrimidine **4a** was obtained in lower yield than in the one-pot process. This second step also requires a base since simple mixing and heating of **2a** and **3a** in the absence of the base lead to the recovery of the starting materials.

In an effort of exemplification, the above one-pot reaction was applied to the synthesis of various complex products by using different dinitriles **1** that were reacted with **3a** to provide a large range of diaminopyrimidine derivatives (Table 2). Due to the presence of side-products arising from self-condensation of **1b** and **1c**, as described in the literature,[17] compounds **4b** and **4c** were obtained in moderate yield (45% and 50%, respectively). Surprisingly, compound **1d** failed to undergo the reaction presumably because seven atom ring formation is penalized under these conditions. In the case of compound **1e**, product **4e** was not isolated because a retro-Michael reaction occurred thus forming the acrylonitrile that polymerized. In contrast, an interesting scaffold was isolated starting from phenylenediacetonitrile **1f** in high yield. The presence of strongly acidic α-protons can explain the high yield of the reaction. Under microwave conditions, the identical reaction afforded compound **4f** in 24% yield in only 2 min of reaction time.

To further exemplify the reaction, we applied it to different cyanamides. Table 3 reports the results of the one-step synthetic pathway starting from **1a** in the presence of various cyanamides **3**. The best yield was obtained with morpholine-4-carbonitrile **3a** to produce compound **4a** in 81% yield. Under the above optimized conditions, the reaction on piperidine-1-carbonitrile **3h** provided compound **4h** in moderate yield (40%) together with side products identified as due to the oligomerization of **3h**.[18] The isolation of compounds **4i** and **4j** showed that various cyclic and non-cyclic cyanamides can react in the one-pot reaction.

Finally, we applied the reaction to a natural product, cytisine, a tricyclic alkaloid described as the reference inhibitor of the α4β2 nicotinic receptor subtype,[19] recently reviewed.[20] Cyanocytisine **3k**, obtained by reaction of cyanogen bromide on cytisine, was engaged in our previously defined conditions and the desired prod-



Scheme 2. Reaction mechanism between PMB-protected dinitrile and a cyanamide.