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Exploring the Scope of DBU-promoted Amidations of 7-carboxymethylpterin

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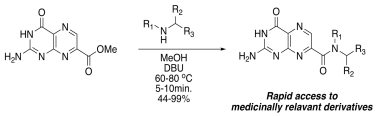
VALPARAISO UNIVERSITY

Abstract

The synthetic utility of pterins is often hampered by the notorious insolubility of this heterocycle, slowing the development of medicinally relevant pteridine derivatives. Reactions which expedite the development of new pterins are thus of great importance. Through a dual role of diazabicycloundecene (DBU), 7-carboxymethylpterin (7-CMP) is converted to the soluble DBU salt, with additional DBU promoting an ester-to-amide transformation. We have explored this reaction to assess its scope and identify structural features in the amines which significantly affect success, monitored the reaction kinetics using a pseudo-first order kinetics model, and further adapted the reaction conditions to allow for product formation in as little as 5 min, with yields often >80%.



Introduction

Pteridines are a class of fused bicyclic heterocycles with significant biological relevance. The core, simply referred to as "pterin", is present in various biological cofactors like folates, biopterin, and molybdopterin.[1] Pterins are an attractive building block in the development of various pharmaceuticals and are used as inhibitors for a multitude of enzymes.[2,3] One major limitation with pterins is their insolubility in most solvents. This can be dealt with by preemptive modifications to the pteridine core which disrupt the hydrogen-bond assembly. Any reaction which expedites the synthesis of pterin derivatives, especially those which bypass the insolubility, is of great importance to both medicinal and supramolecular chemists.

Utilizing a previously developed DBU-promoted reaction can help with rapidly making new pterins (**Figure 1**).[4] With the addition of DBU, the DBU salt is formed which aides in increasing the solubility of pterins. Additionally, DBU plays a role in improving the ester-to-amide transformation. As a result, a large library of pterin amides can be generated quickly and smoothly.

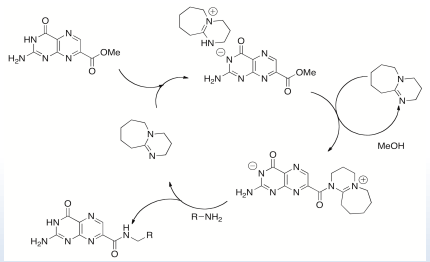


Figure 1. A route to new pterin amides.

General Process

The general reaction is seen in **Figure 2.** The starting material is a previously synthesized 7-CMP. With the addition of methanol, DBU and an amine of choice the reaction can easily produce the amide products. For efficient time, the best conditions ranged between about 5-10 min and 60-80 °C.[5]

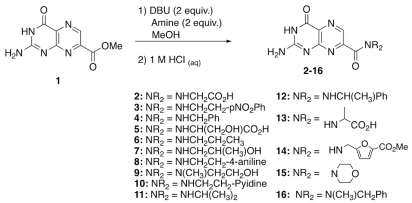


Figure 2. The general DBU-promoted reaction with 7-CMP and amide.

Reaction Optimization with Benzylamine

To assist in the optimizing of reaction conditions, Benzylamine was used as a representative example. The only two variables being changed were the temperature and the time of the run. The temperature was monitored using a microwave reactor. The optimal condition was found to be about 60°C for 5 minutes (**Table 1**).

Temp (°C)	Time (min)	Yield (%)
110	30	78
110	20	90
80	30	89
80	10	90
60	10	91
60	5	91
60	1	44
40	5	46

Table 1. Conditions tested using Benzylamine.

Additional Amine Screening

After the determination of ideal conditions, a series of amines were tested (**Table 2**). The effectiveness of the reaction is mostly affected by **α**-substitution on the amine. This can be seen in 1-propylamine vs isopropylamine, or Glycine vs Alanine, among other examples. The less steric hinderance the lower the temperature, shorter time, and higher the percent yield. In addition to **α**-substitution, another steric effect that negatively affected the reaction was additional substitution on the amine nitrogen. The secondary amine N-methyl-benzylamine was virtually unreactive under our typical reaction conditions.

Amine Tested	Conditions[a]	Yield (%)
Glycine	60 °C; 5 min	99
4-nitro-phenethylamine	60 °C; 5 min	96
Benzylamine	60 °C; 5 min	91
Serine	60 °C; 5 min	88
1-propylamine	60 °C; 5 min	87
1-amino-2-propanol	60 °C; 5 min	85
4-Aminoethyl-aniline	60 °C; 5 min	76
N-methylamino-ethanol	60 °C; 5 min	71
Aminoethyl pyridine	60 °C; 5 min	66
Isopropylamine	80 °C; 10 min	66
α-methylbenzylamine	80 °C; 10 min	60
Alanine	80 °C; 10 min	49
Methyl 2-Aminomethyl 5-furanoate	60 °C; 5 min	47[b]
Morpholine	80 °C; 20 min	44
N-methyl-benzylamine	60 °C; 5 min	63[c]

[a]Typical conditions: 2eq. amine, 2eq DBU, sealed reaction vessel
[b]Low yield for this amine was due to side reaction
[c]No reaction under typical conditions. 10equiv. amine used.

Table 2. Screen results for different amines tested.

As stated, sterics negatively effect this reaction. However, if the amine contains a β-hydroxy group this hinderance can be overcome and expedite the process due to the hydrogen bonding to the 7-CMP that takes place, which accelerates this amidation (**Figure 3**). This effects is seen in Serine vs Alanine, or N-methylamino-ethanol vs N-methyl-benzylamine.

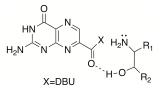


Figure 3. Effect of β-hydroxy group in improving rate of reaction

NMR Study

To better understand how the amine's structure influenced the reaction rate, the reaction was monitored using NMR spectrometry to quantify the rate of product formation (**Figure 4**). From this data the rate of the reaction could be analyzed using pseudo first-order kinetics, giving rate constants for key amines (**Table 3**). These results further illustrate how the **α**-substitution and the presence of a β-hydroxy group impact the outcome of the reaction.

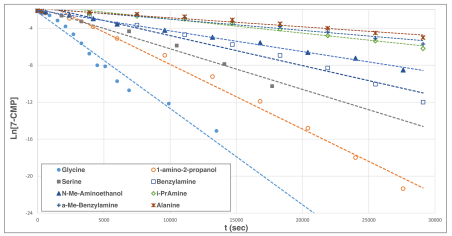


Figure 4. NMR results of the pseudo first-order reactions with different amines.

Amine	k @ 22°C (M^{-1} s^{-1})	Amine	k @ 22°C (M^{-1} s^{-1})
Glycine	$3.4x10^{-3}$	N-methyl-aminoethanol	$0.78x10^{-3}$
1-amino-2-propanol	$2.3x10^{-3}$	Isopropyl amine	$0.61x10^{-3}$
Serine	$1.5x10^{-3}$	α-methyl benzylamine	$0.57x10^{-3}$
Benzylamine	$1.1x10^{-3}$	Alanine	$0.45x10^{-3}$

Values determined by first finding k_{obs} from pseudo-first order kinetic plot

Table 3. Rate constants determined by 1H-NMR kinetics

Conclusions

The DBU-promoted amidation of 7-methoxycarbonylpterin is a useful method for rapidly generating new pterin derivatives, for medicinal or supramolecular purposes. This benefits from its ability to bypass the notorious insolubility of pterins in most solvents. We have shown this reaction also benefits in its ease and often rapid reaction times (typically 5–10 min). While this amidation reaction can be hindered by typical steric effects, we have shown these issues are largely overcome in amines with additional hydrogen-bonding substituents like a β-hydroxy group. As such, the DBU amidation of 7-CMP can be viewed as an essential tool for heterocyclic chemists.

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