

Type of the Paper (Abstract, Meeting Report, Preface, Proceedings, etc.)

A microwave-assisted synthesis of 3-(5-amino-1*H*-1,2,4-triazol-3-yl)propanamides from succinimides [†]

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Abstract: 1,2,4-Triazole is a privileged scaffold in medicinal and agricultural chemistry. Many useful and structurally diverse compounds have been prepared using 5-amino-1,2,4-triazoles as building block. Herein, we report a new microwave-assisted synthesis of 3-(5-amino-1*H*-1,2,4-triazol-3-yl)propanamides *via* two complementary approaches. The first approach involved the initial preparation of *N*-guanidinosuccinimide, which then reacted with amines under microwave irradiation affording corresponding 3-(5-amino-1*H*-1,2,4-triazol-3-yl)propanamides. The desired products were successfully obtained in the reaction with aliphatic amines (primary and secondary) *via* a nucleophilic opening of the succinimide ring and the subsequent recyclization affording the 1,2,4-triazole ring. This approach failed when less nucleophilic aromatic amines were used. Therefore, we designed an alternative pathway with the initial preparation of *N*-arylsuccinimides and their subsequent reaction with aminoguanidine hydrochloride under microwave irradiation. In this case, the 1,2,4-triazole ring closure was most efficiently achieved in the presence of organic base. These two approaches complement each other allowing preparation of a diverse library of 3-(5-amino-1*H*-1,2,4-triazol-3-yl)propanamides.

Keywords: microwave-assisted synthesis; triazole; succinimide; *N*-arylsuccinimides.

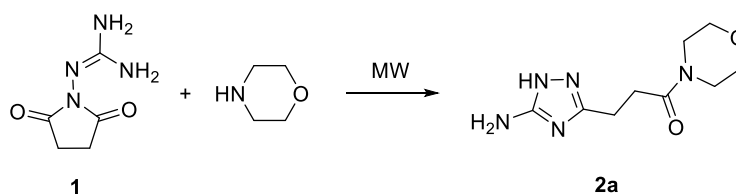
1. Introduction

1,2,4-Triazoles attract significant attention of researchers due to their useful medicinal properties [1]. There have been continuous attempts to develop new and improve existing methods for the preparation of 1,2,4-triazoles [2]. However, synthetic methods available for the preparation of 3-(5-amino-1*H*-1,2,4-triazol-3-yl)alkanamides are limited and possess several drawbacks [3]. Hence, there is an ongoing need for the development of practical and efficient methods for their synthesis. Nowadays, utility of microwave irradiation in organic chemistry has been favourable following the successful preparation of various biologically active compounds from microwave-assisted synthesis [4]. Herein, we report a successful approach in using microwave irradiation for the preparation of a library of 3-(5-amino-1*H*-1,2,4-triazol-3-yl)propanamides *via* two complementary approaches.

2. Results and Discussion

In our model reaction of *N*-guanidinosuccinimide (**1**) and morpholine, we adopt the general approach proposed by Chernyshev & Chernysheva. [5]. In an attempt to improve the efficiency of the reaction, the synthesis of *N*-morpholino-3-(5-amino-1*H*-1,2,4-triazol-3-yl)propanamide (**2a**) *via* cyclic amide ring opening and recyclization to the 1,2,4-triazole was conducted under microwave irradiation (Table 1). Initially, we attempted the reaction of **1** with morpholine in ethanol under microwave irradiation at 180 °C for 25 min (Entry 1). We successfully obtained the desired product **3a** in high purity after simple filtration, but the yield was rather low (27%). Screening of solvents revealed that conducting the reaction in polar aprotic solvents (Entries 2 and 3) generally led to a better yield compared to the reaction in polar protic solvents (Entries 1 and 4). Further optimisation of the reaction conditions, we found that decreasing the reaction temperature to 170 °C led to an improvement in yields (Entry 5). However, altering the time of reaction did not lead to any improvement in outcome (Entries 7 and 8). Varying reagent ratio also did not increase the yield of the reaction (Entries 9 and 10). With our optimized conditions, we then attempted to scale up the reaction from 1 mmol to 10 mmol. Under identical conditions, the reaction afforded the same high purity product **3a** in good yield (88%)

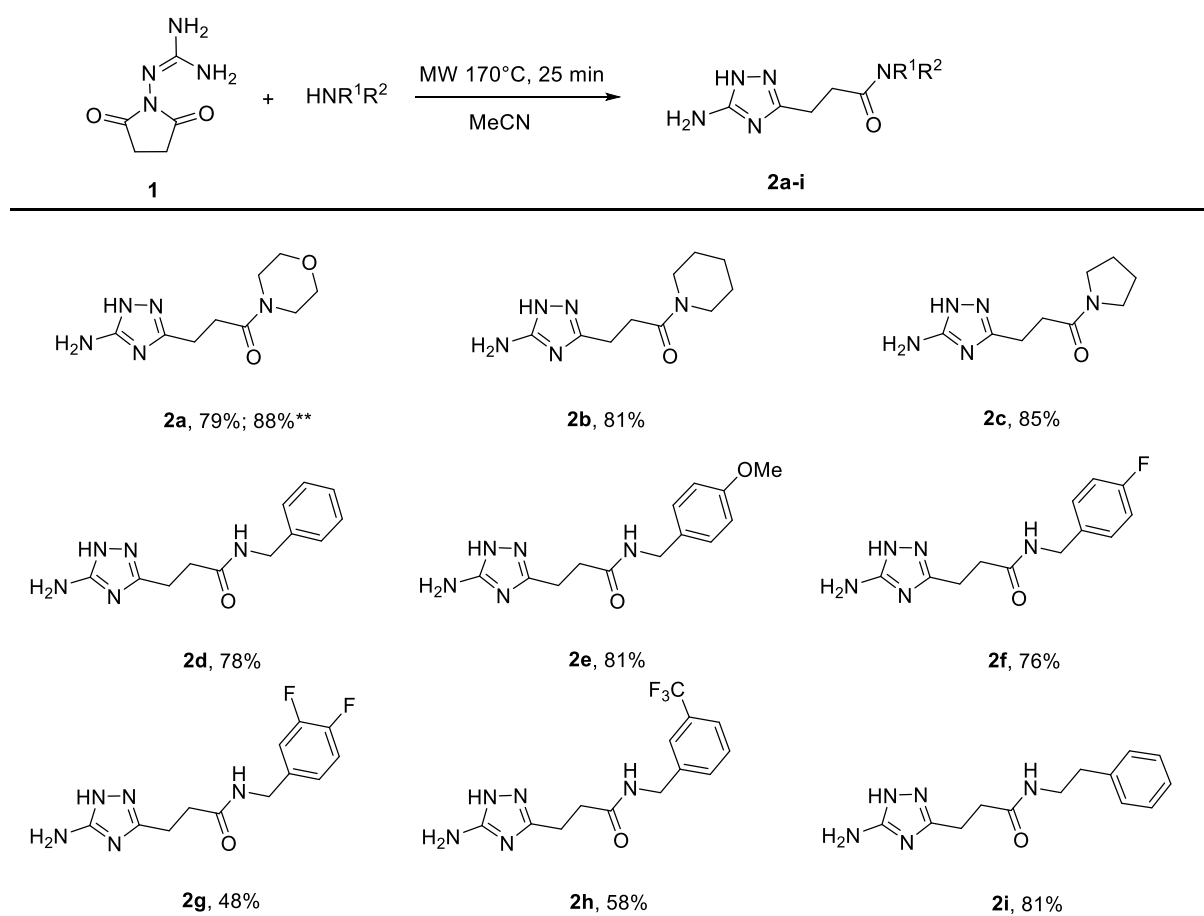
Table 1. Optimization of conditions for the synthesis of *N*-morpholino-3-(5-amino-1*H*-1,2,4-triazol-3-yl)propanamide (**2a**)*



Entry	Solvent	Ratio of 1: morpholine	Temperature (°C)	Time (min)	Isolated yield (%)
1	EtOH	1 : 2	180	25	27
2	EtOAc	1 : 2	180	25	64
3	MeCN	1 : 2	180	25	75
4	H ₂ O	1 : 2	180	25	28
5	MeCN	1 : 2	170	25	79
6	MeCN	1 : 2	160	25	65
7	MeCN	1 : 2	170	30	73
8	MeCN	1 : 2	170	20	73
9	MeCN	1 : 3	170	25	68
10	MeCN	1 : 1.5	170	25	66

* The reaction was performed using a Discover SP CEM microwave synthesizer with 1 mmol of **1** in 1 mL of the specified solvent.

The scope of the method was explored using various amines. The reaction proceeded well with a series of aliphatic amines (primary and secondary). The optimized conditions for the preparation of **2a** were successfully applied for the synthesis **2b-i** allowing the preparation of a diverse library of *N*-alkyl- and *N*-aryllalkyl-3-(5-amino-1*H*-1,2,4-triazol-3-yl)propanamides (Table 2).

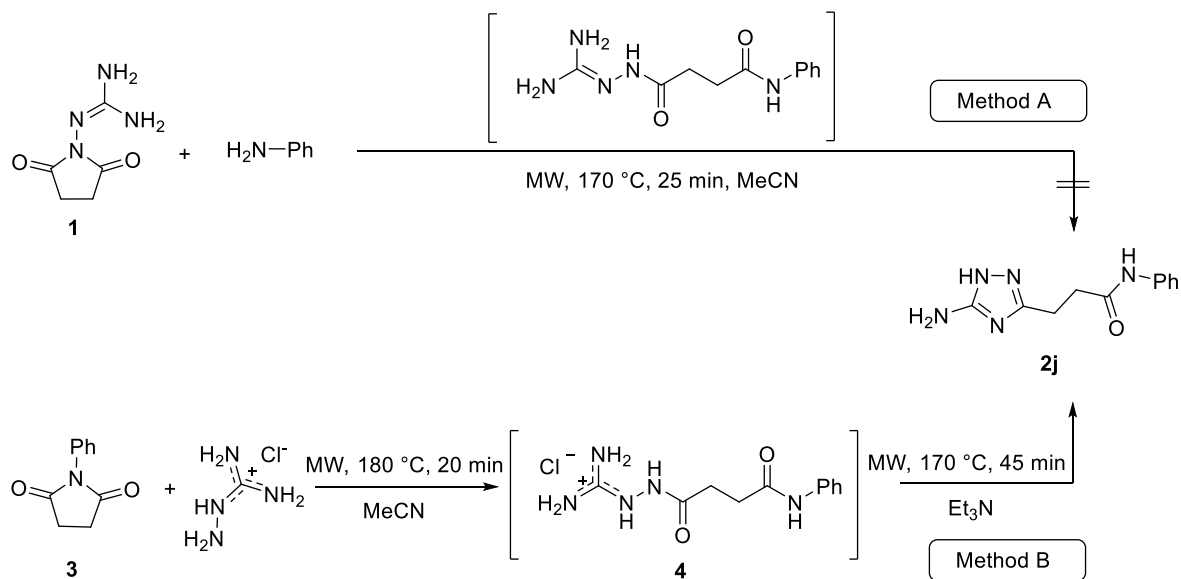
Table 2. Microwave-assisted synthesis of 3-(5-amino-1*H*-1,2,4-triazol-3-yl)propanamides (**3a-i**)*

* The reaction was performed using a Discover SP CEM microwave synthesizer with 1 mmol of *N*-guanidinosuccinimide (**1**) and 2 mmol of specified amine at 170°C for 25 minutes in 1 mL of the acetonitrile.

** The reaction was performed with 10 mmol *N*-guanidinosuccinimide (**1**) and 20 mmol of morpholine at 170°C for 25 minutes in 10 mL of the acetonitrile.

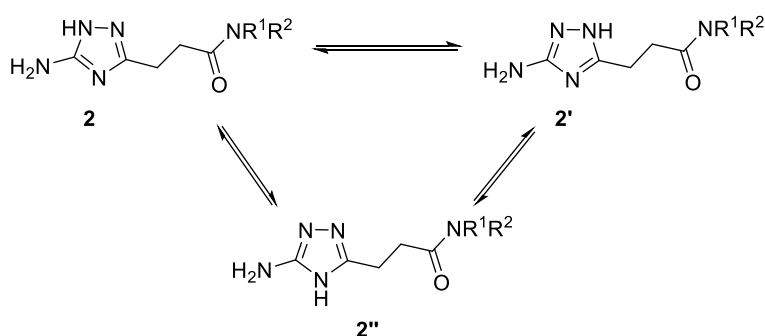
In our attempt to involve aniline in this reaction with *N*-guanidinosuccinimide (**1**) under similar conditions, formation of the desired product was not detected (Scheme 1, Method A). Analysis of the reaction mixture revealed the presence of aniline and unreacted **1**. Therefore, the rate determining step involving nucleophilic opening of the *N*-guanidinosuccinimide ring by amines was found to limit the scope of this method. In comparison to aliphatic amines, the nucleophilicity of aniline is not sufficient to initiate the reaction under these conditions. To overcome this limitation, an alternative pathway was designed for the preparation of *N*-phenyl-3-(5-amino-1*H*-1,2,4-triazol-3-yl)propanamide (**2j**) via reaction of *N*-phenylsuccinimide with aminoguanidine hydrochloride (Scheme 1, Method B).

The reaction was performed in a one-pot manner with *N*-phenylsuccinimide (**3**) and aminoguanidine hydrochloride forming ring-opened intermediate **4** followed by the triazole ring closure upon the treatment with base. The reaction was carried out under microwave irradiation and successfully furnished in the formation of desired compound **2j** in the 66% overall yield. Therefore, this approach efficiently complements the initial approach and allows further expansion of the library of 3-(5-amino-1*H*-1,2,4-triazol-3-yl)propanamides. The exploration of the scope of the Method B is ongoing.



Scheme 1. Microwave-assisted synthesis of **2j**

In the NMR spectroscopy data, particularly the broadening of signals for the C-3 and C-5 of the 1,2,4-triazole ring atoms in ^{13}C NMR spectra indicates annular prototropic tautomerisation of the compounds with forms **2**, **2'**, **2''** possible. (Scheme 2).



Scheme 2. Tautomeric forms of **2**.

3. Conclusions

In conclusion, we developed microwave-assisted method for the preparation of diverse 3-(5-amino-1H-1,2,4-triazol-3-yl)propanamides *via* two complementary synthetic approaches.

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