Three-step, One-pot Microwave Assisted Synthesis of 3-Thio-1,2,4-triazoles

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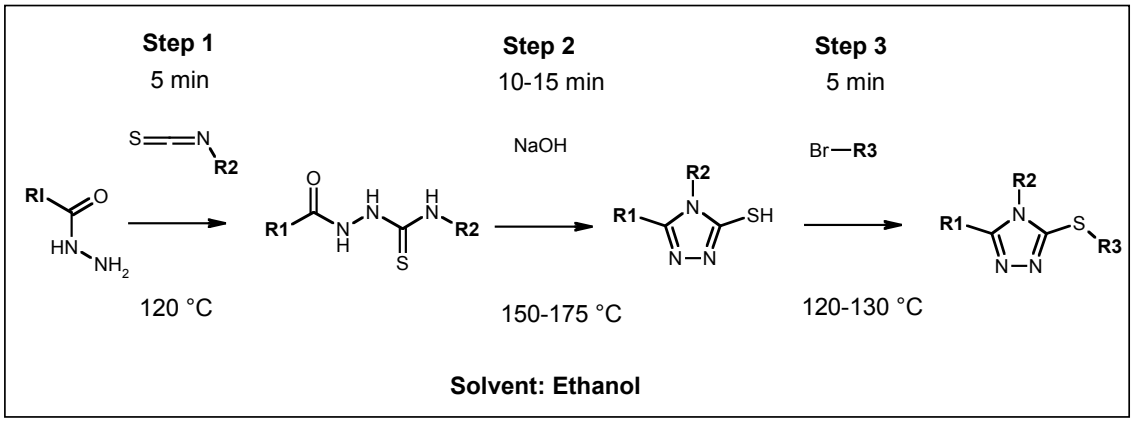
Introduction

3-thio-1,2,4-triazoles can be found as templates in several biologically active compounds,[1] and have also been used as amide isosteres in the synthesis of peptidic antagonists.[4] The well known conventional synthesis, described both in solution[2] and on solid-phase,[3] is performed in three steps. In the first step condensation of isothiocyanate with acyl hydrazide gives hydrazinecarbothiamide. In the subsequent cyclisation step, 3-mercapto-1,2,4-triazole is formed. The target compound is obtained after S-alkylation in the third step.

In a recently reported solution synthesis,[4] the three step reaction sequence required a total duration of more than 26 hours. Step one and three were carried out at room temperature and step two at 85 °C. A solvent change was required after the first step and polymer-supported BEMP was used as deprotonating reagent in the last alkylation step.

In this poster we present a three-step, one-pot microwave assisted synthesis of 3-thio-1,2,4-triazoles with a total reaction time of 20-25 minutes. The synthesis was performed without solvent change, and the excess of sodium hydroxide used in the cyclisation step was sufficient to deprotonate the thiol and obtain alkylation in step three. (Scheme).



Scheme

Results and Discussion

In order to produce a small library of 3-thio-1,2,4-triazoles, four acyl hydrazides, two isocyanates and two bromides were chosen (Table 1).

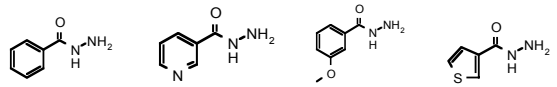
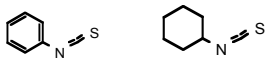
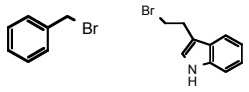
Acyl hydrazides	
Isothiocyanates	
Bromides	

Table 1

Entry	Acyl Hydrazide **R1**	Isothiocyanate **R2**	Bromide **R3**	Overall Isolated yield, %	LCMS purity 254 nm %
1	Phenyl	Phenyl	Benzyl	**76**	98
2	Phenyl	Phenyl	2-(3-indolyl)ethyl	**74**	98
3	Phenyl	Cyclohexyl	Benzyl	**70**	99
4	Phenyl	Cyclohexyl	2-(3-indolyl)ethyl	**68**	98
5	3-Pyridyl	Phenyl	Benzyl	**69**	97
6	3-Pyridyl	Phenyl	2-(3-indolyl)ethyl	**77**	98
7	3-Pyridyl	Cyclohexyl	Benzyl	**54**	99
8	3-Pyridyl	Cyclohexyl	2-(3-indolyl)ethyl	**60**	97
9	3-MeO-Phenyl	Phenyl	Benzyl	**77**	98
10	3-MeO-Phenyl	Phenyl	2-(3-indolyl)ethyl	**80**	97
11	3-MeO-Phenyl	Cyclohexyl	Benzyl	**73**	98
12	3-MeO-Phenyl	Cyclohexyl	2-(3-indolyl)ethyl	**67**	96
13	2-Thienyl	Phenyl	Benzyl	**63**	97
14	2-Thienyl	Phenyl	2-(3-indolyl)ethyl	**61**	97
15	2-Thienyl	Cyclohexyl	Benzyl	**58**	93
16	2-Thienyl	Cyclohexyl	2-(3-indolyl)ethyl	**58**	96

Table 2

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In the first condensation step, acid hydrazide and isothiocyanate, were heated by microwaves at 120 °C for 5 minutes with ethanol as solvent, affording the hydrazinecarbothioamide intermediate. After this step LCMS analysis of the reaction mixture showed almost complete conversion for all sixteen reactions. The second step, cyclisation to mercaptotriazole, was carried out by adding 1 M NaOH in excess to the reaction mixture from step 1 and heating by microwaves. A reaction temperature of 150 °C for 10 min proved to be sufficient when phenylisothiocyanate was used in step 1, while a higher temperature, 175 °C, and a longer reaction time, 15 min, was necessary when cyclohexylisothiocyanate was used. The final third step, S-alkylation, was performed by simply adding the bromide to the prior reaction mixture and heating in microwaves at 120 °C (benzylbromide) or 130 °C (3-(2-bromoethyl)indole) for 5 minutes.

The final reaction mixtures from step 3 were worked up by adding water and then extracting with ethyl acetate. Evaporation of the extracts gave the crude products. The crude materials were subsequently purified by flash chromatography. The isolated yields over 3 steps were in the interval 54-80 % (Table 2), which means an average yield/step between 81 % and 93 %.
The purity of the isolated products were in the interval 93-99 % measured with LC-MS at 254 nm (Table 2). The structures of the isolated products were confirmed by ^{1}H-NMR.

General experimental procedure

All microwave heatings were performed on an Emrys Optimizer™ or an Initiator™sixty from Biotage.

Step1: A 0.5-2 ml microwave vial loaded with a mixture of 0.25 mmol acid hydrazide, 0.26 mmol isothiocyanate and 1.5 ml ethanol was capped and heated to 120 °C for 5 minutes. After cooling, the vial was decapped.
Step 2: To the resulting ethanol solution 0.40 ml 1M NaOH in water (0.4 mmol) was added. The vial was capped and heated again to 150 °C (when R2=phenyl) or 175 °C (when R2=cyclohexyl) for 10 minutes or 15 minutes respectively. After cooling, the vial was decapped.
Step 3: To the resulting reaction mixture 0.275 mmol bromide was added. The vial was capped and heated again to 120 °C (when R3=benzyl) or 130 °C (when R3=2-(3-indolyl)ethyl) for 5 minutes. After cooling, the vial was decapped.
Work-up and purification: 2 ml of water was added to the final reaction mixture. The suspension was extracted with 10 ml of ethyl acetate. The extract was concentrated and the residue purified by chromatography on a Horizon™ HPFC™ System using a FLASH 12+M prepacked silica cartridge. The purified products were analysed by LCMS and characterised by ^{1}H-NMR.

Conclusion

In this poster we present a three-step, one-pot microwave assisted synthesis of 3-thio-1,2,4-triazoles. The synthesis sequence was performed in a substantially shorter total reaction time than for a reported conventional synthesis; 20-25 minutes versus 26 hours. The synthesis was carried out without isolation of the intermediates and, moreover, no solvent change between the three steps was necessary; the reagents were simply added to the reaction mixture between the heatings. No specific deprotonating agent was required in the last alkylation step. A moderate excess of base in the preceding cyclisation step was sufficient for alkylation. After finishing the synthesis sequence, an easy work-up and a subsequent flash chromatography resulted in high purity 3-thio-1,2,4-triazoles, 93-99 % by LCMS. The products were characterised by ^{1}H-NMR. The total isolated yields over 3 steps were in the interval 54-80 % which implies average yields/step between 81 % and 93 %.

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