Two-step, One-pot Synthesis of 5-Aryl-2-Amino-1,3,4-Oxadiazoles Using Microwave-assisted Synthesis

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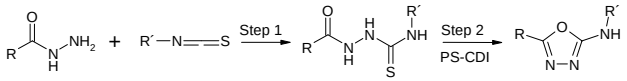
Introduction

Oxadiazoles are a class of compounds that possess interesting biological activity. Coppo *et al*[1] have recently described a two step, one pot method for the synthesis of 5-substituted-2-amino-1,3,4-oxadiazoles (*Scheme 1*) in solution.



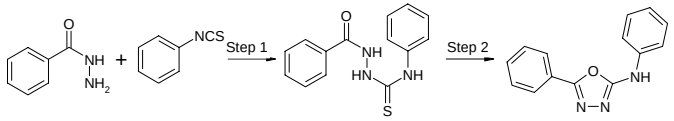
Scheme 1.

The first step is straightforward, but the second step, the cyclodesulfurisation, can be achieved by several methods, including I_2/NaOH, carbodiimides and mercury-salts. Coppo *et al* used a very elegant method with resin-bound carbodiimide, that can easily be filtered off. The drawback of this method is the long reaction times. The first step takes 20 hours at room temperature. The second step takes about 40-80 hours, including 20 hours scavenging the reaction mixture with added silica-bound propylamine and polystyrene-bounded-BEMP. The solid-phase scavengers are added to remove excess isothiocyanate and unreacted starting material in Step 2. In total, 1.5-4 days reaction times are required for this two step method.

In 2002, Wang *et al*[2] performed the cyclodesulfurisation step with mercury(II) acetate by microwave heating. We decided to investigate if we could shorten the reaction times using microwaves, retaining the benefits of solid-phase reagents. Furthermore, we wanted to examine if the scavenging steps could be omitted.

Results and discussion

The reaction (*Scheme 2*) presented in the publication was choosen as model reaction to be optimised with reference to time and temperature on Emrys™ Optimizer.



Scheme 2.

For the first step, optimisation experiments revealed 98 % conversion (by HPLC-MS) in 5 minutes at 120 °C, when reacting 1.00 equivalent benzhydrazide with 1.05 equivalents phenyl isothiocyanate using *N*,*N*-dimethylformamide as solvent. Under these conditions only 0.5% benzhydrazide was left, and an impurity (1.0%) appeared. Prolonged reaction time and/or higher temperature resulted in decomposition of the product. Using dichloromethane or acetonitrile as solvent did not give complete reaction, even at prolonged reaction times.

Encouraged by these results, we decided to run several reactions with different substituted arylhydrazides and isothiocyanates (*Sceme 1*) in order to examine the generality of this method (*Table 1, General Experimental Procedure-Step 1*).

R	R´	LC-purity (%)	MS M+1
Ph	Ph	98	272
Ph	4-NO_2-Ph	92	317
Ph	2-MeO-Ph	94	302
Ph	2-Toluyl	94	286
Ph	4-CN-Ph	96	297
3-Pyridyl	2-Br-Ph	88	351*
3-Pyridyl	Bn	98	287
3-Pyridyl	4-F-Ph	93	291
3-Pyridyl	3-Pyridyl	97	274
3-MeO-Ph	Ph	98	302
3-MeO-Ph	Bn	99	316
3-MeO-Ph	2-Br-Ph	96	280*
3-MeO-Ph	4-F-Ph	96	320
3-MeO-Ph	3-Pyridyl	96	303
3-MeO-Ph	2-CF_3-Ph	97	370

Table 1. Step 1.
*Only M^+-isotope

Adding 1.10 equivalents of polystyrene-bounded carbodiimide to the reaction mixture (from *Step 1*), followed by heating with microwaves to 150 °C for 5 minutes, resulted in 99% conversion (94% purity by HPLC-MS) for the second step. Using silica-bounded carbodiimide (1.05 mmol/g) gave less conversion and at least five new impurities. After filtration and concentration, the desired crude product was obtained. ^{1}H-NMR spectrum on this crude product revealed that it contained traces of impurities along with material which was released by the polymer support (several signals at 1-2 ppm). Slurrying the crude material in a small amount of acetonitrile following by filtration, removed all impurities. Thus the desired compound was obtained in 86% yield and 100% purity (by HPLC-MS and ^{1}H-NMR), compared to 67 and 96% respectively in the publication.[1]

General Experimental Procedure

Step 1. A 10 mL reaction vial loaded with a mixture of 0.500 mmol aryl hydrazide, 0.525 mmol isothiocyanate and 3.00 mL DMF, was capped and heated to 120 °C in Emrys Optimizer 5 minutes. After cooling, the vial was decapped and the mixture was analysed by HPLC-MS (*Table 1*).

Step 2. To the resulting solution was added 1.10 mmol polystyrene-bounded carbodiimide (0.94 mmol/g) and the mixture was heated to 150 °C in Emrys Optimizer for 5 minutes. After cooling, the vial was decapped and the mixture was analysed by HPLC-MS (*Table 2*). The solid phase reagent was filtered off and washed with 10 mL boiling ethanol. The resulting solution was concentrated and the solid residue was slurried in the solvent stated in *Table 2*. The solid was filtered off, washed with 5 mL solvent, dried under vaccum and analysed by HPLC-MS and characterised by ^{1}H-NMR.

Conclusion

In this poster, a two-step, one-pot method for the synthesis of 5-aryl-2-amino-1,3,4-oxadiazoles is described. This method dramatically shortens the reaction times from days to only 10 minutes, by heating the reaction mixtures with microwaves.
Using this method, scavengers for removing the reactants and the formed intermediates can be omitted. Due to the high purity of the crude materials, the purification of the products can be limited to slurrying the crude materal in an appropriate solvent.

R	R´	Isolated yield (%)	HPLC-purity 254 nm (%)	HPLC-purity 214 nm	MS M+1
Ph	Ph	86*	100	99.8	238
Ph	4-NO_2-Ph	92**	100	100	283
Ph	2-MeO-Ph	88*	100	100	268
Ph	2-Toluyl	96**	100	99.4	252
Ph	4-CN-Ph	95**	100	100[a]	263
3-Pyridyl	2-Br-Ph	87**	100	100	317[b]
3-Pyridyl	Bn	90*	100	97.5	253
3-Pyridyl	4-F-Ph	76**	100	100[c]	257
3-Pyridyl	3-Pyridyl	93**	100	100[d]	240
3-MeO-Ph	Ph	87**	100	100	268
3-MeO-Ph	Bn	85*	93.8	95.7	282
3-MeO-Ph	2-Br-Ph	91*	100	99.5	346[b]
3-MeO-Ph	4-F-Ph	89**	100	100	286
3-MeO-Ph	3-Pyridyl	93**	100	99.6	269
3-MeO-Ph	2-CF_3-Ph	88***	96.7	93.9	336

Table 2. Step 2.
a= 314 nm, b= only M^+-isotope, c= 300 nm, d= 240 nm
*Slurried in acetonitrile, ** Slurried in acetone, ***Slurried in ethanol

References:
1. Coppo, F.T.; Evans, K.A.; Graybill, T.L. and Burton. G. *Tetrahedron Letters* 2004, **45**, 3257

2. Wang, X.; Li, Z.; Wei, B. and Yang, J. *Synth. Commun*. 2002, **32**, 1097

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