Convenient Synthesis of 5-Substituted-2-Amino-1,3,4-Oxadiazoles Using Microwave Heating

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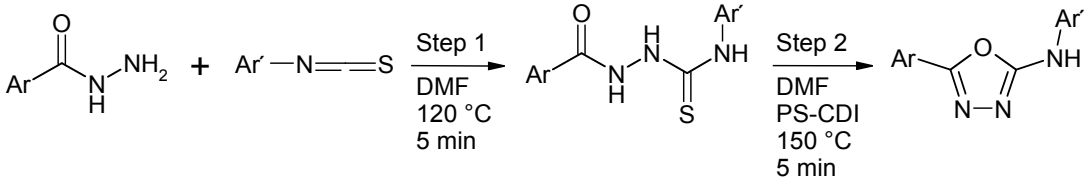
Introduction

Coppo *et al*[1] have recently described a two step, one pot method for the synthesis of 5-aryl substituted-2-amino-1,3,4-oxadiazoles in solution.
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 of scavenging the reaction mixture with added silica-bound propylamine and polystyrene-bounded BEMP.
We have lately presented a work where both steps were heated by microwaves (*Scheme 1*), thus shortening the reaction time to only 10 minutes.[2]

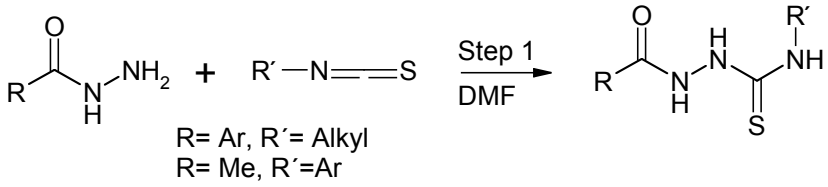


Scheme 1.

In order to investigate the impact of the substituents, we decided to run a library without the simultaneous use of aryl substituents both on the hydrazide and the isothiocyanate moiety.

Results and discussion

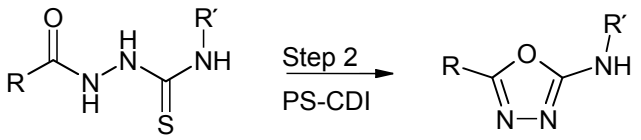
Using an aryl hydrazide and an aliphatic isothiocyanate (*Scheme 2*) for the first step, optimization experiments revealed that the temperature must be increased to 140 °C and the reaction time extended to 10 min, when reacting hydrazide with 1.05 equivalents of isothiocyanate using *N*,*N*-dimethylformamide as solvent (*Table 1*). Having the sterically hindered tertiary butylisothiocyanate as electrophile, optimization resulted in that the temperature should be decreased to 100 °C, and the amount of isothiocyanate increased to 2.00 equiv. Using acethydrazide as nucleophile, only 1.05 equivalents of isothiocyanate was needed, and the temperature and reaction time could be decreased to 120 °C and 5 min, respectively.



Scheme 2.

Biotage

Adding 1.10 equivalents of polystyrene-bound carbodiimide to the reaction mixture from Step 1 (*Scheme 2*) followed by heating with microwaves to 160 °C for 15 minutes (*Scheme 3*), resulted in complete conversion for the second step (*Table 2*).



R= Ar, R´= Alkyl
R´= Me, R´= Ar

Scheme 3.

R	R´	Time (min)	Temp (°C)	HPLC-purity (%)	MS M+1
3-MeO-Ph	Ethyl	10	140	98.9	254
3-MeO-Ph	Propyl	10	140	99.1	268
3-MeO-Ph	Cyclohexyl	10	140	96.1	308
3-MeO-Ph	Allyl	10	140	99.2	266
3-MeO-Ph	CH_2COOEt	10	140	97.1	312
Ph	Ethyl	10	140	99.3	224
Ph	Cyclohexyl	10	140	97.0	278
Ph	Allyl	10	140	98.5	236
Ph	CH_2COOEt	10	140	96.4	282
3-Pyridyl	Ethyl	10	140	99.5	225
3-Pyridyl	Cyclohexyl	10	140	89.9	279
3-Pyridyl	Allyl	10	140	99.3	237
3-Pyridyl	CH_2COOEt	10	140	99.4	283
2-Furyl	Ethyl	10	140	98.2	214
2-Furyl	Cyclohexyl	10	140	91.0	268
2-Thienyl	Allyl	10	140	99.3	242
2-Thienyl	CH_2COOEt	10	140	96.2	288
3-MeO-Ph	tert. Butyl	15	100	90.9	282
Ph	tert. Butyl	15	100	91.3	252
3-Pyridyl	tert. Butyl	15	100	85.2	253
2-Furyl	tert. Butyl	15	100	88.9	242
2-Thienyl	tert. Butyl	15	100	87.3	-[a]
Me	2-MeO-Ph	5	120	77.7	240
Me	Ph	5	120	74.6	210
Me	Bn	5	120	93.6	224
Me	3-Pyridyl	5	120	76.2	-[a]
Me	4-NO_2-Ph	5	120	-[a]	255

Table 1. Step 1.
a= No satisfactory UV-trace or m/z could be obtained

Biotage

Products from Step 1 including the tertiary butyl moiety required lower temperature (140 °C) and extended reaction time (20 min) since decomposition occurred at elevated temperatures. Products from Step 1 including the aceto moiety required lower temperature (150 °C) and shorter reaction time (5 min) to give complete conversion. After filtration and concentration, the desired crude products were obtained. Purification of the crude products by chromatography on Horizon HPFC System using a Biotage FLASH+ prepacked silica cartridge, or by slurrying the crude material in a small amount of ethyl acetate or acetonitrile followed by filtration, gave the isolated products (*Table 2*).

General Experimental Procedure

Step 1. A 10 mL reaction vial loaded with a mixture of 0.500 mmol hydrazide, 0.525 mmol (or 1.00 mmol for the products containing the tertiary butyl moiety) isothiocyanate and 3.00 mL DMF, was capped and heated in Emrys Optimizer to the temperature and for the time stated in *Table 1*. After cooling, the vial was decapped and the mixture was analyzed by HPLC-MS (*Table 1*).

R	R´	Time (min)	Temp (°C)	Eluent System[a]	Yield (%)	Purity (%)[e]
3-MeO-Ph	Ethyl	15	160	1:3	47	99.8
3-MeO-Ph	Propyl	15	160	1:2	46	99.3
3-MeO-Ph	Cyclohexyl	15	160	1:1	45	100
3-MeO-Ph	Allyl	15	160	2:1	43	98.0
3-MeO-Ph	CH_2COOEt	15	160	2:1	41	98.2
Ph	Ethyl	15	160	2:3	41	98.2
Ph	Cyclohexyl	15	160	1:1	40	97.6
Ph	Allyl	15	160	1:1	43	98.8
Ph	CH_2COOEt	15	160	1:1	44	89.0
3-Pyridyl	Ethyl	15	160	25:1[b]	36	99.1
3-Pyridyl	Cyclohexyl	15	160	25:1[b]	42	98.6
3-Pyridyl	Allyl	15	160	20:1[b]	47	99.3
3-Pyridyl	CH_2COOEt	15	160	25:1[b]	40	100
2-Furyl	Ethyl	15	160	1:2	47	100
2-Furyl	Cyclohexyl	15	160	1:1	43	99.4
2-Thienyl	Allyl	15	160	1:1	46	91.0
2-Thienyl	CH_2COOEt	15	160	1:1	41	94.5
3-MeO-Ph	tert. Butyl	20	140	2:1	39	99.0
Ph	tert. Butyl	20	140	2:1	40	94.7
3-Pyridyl	tert. Butyl	20	140	2:3	36	100
2-Furyl	tert. Butyl	20	140	3:2	36	97.8
2-Thienyl	tert. Butyl	20	140	2:1	33	100
Me	2-MeO-Ph	5	150	2:3	59	99.6
Me	Ph	5	150	-[c]	56	99.5
Me	Bn	5	150	1:4	35	100
Me	3-Pyridyl	5	150	-[d]	66	100
Me	4-NO_2-Ph	5	150	-[d]	57	98.9

Table 2. Step 2.
a= Heptane-EtOAc, b= CH_2Cl_2-MeOH, c= Slurried in EtOAc, d= Slurried in CH_3CN
e= HPLC at 254 nm

Biotage

Step 2. To the resulting solution was added 0.550 mmol polystyrene-bound carbodiimide (0.94 mmol/g) and the mixture was heated in Emrys Optimizer to the temperature and the time stated in *Table 2*. After cooling, the vial was decapped and the mixture was analyzed by HPLC-MS. The solid phase reagent was filtered off and washed with 10 mL boiling ethanol. The resulting solution was concentrated and the residue was purified by chromatography on Horizon HPFC System using a Biotage FLASH+ prepacked silica cartridge (eluent: see *Table 2*), or by slurrying the crude material in a small amount of ethyl acetate or acetonitrile followed by filtration. All products were isolated, dried under vacuum and analyzed by HPLC-MS and characterized by ^{1}H-NMR.

Conclusion

In this poster, a two-step, one-pot method for the synthesis of 5-substituted-2-amino-1,3,4-oxadiazoles is described. This method dramatically shortens the reaction times from days to only minutes, by heating the reaction mixtures with microwaves.

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

2. Panagiotis Ioannidis and Ronny Lundin
229th ACS National Meeting & Exposition March 13-17th, 2005, San Diego, CA

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