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An efficient synthesis of rufinamide, an antiepileptic drug

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ABSTRACT

A two-step, one-pot synthesis of rufinamide, an antiepileptic drug, has been developed. 2,6-Difluorobenzyl azide reacts with methyl 3-methoxyacrylate followed by methanolic ammonia to afford rufinamide in 89% yield. The new method generates less waste and uses reagents that are both less expensive and less toxic than other reported syntheses.

1. Introduction

Epilepsy is a neurological disorder that is characterized by recurrent seizures. Approximately 50 million people worldwide suffer from one of the more than 40 different forms of epilepsy. Most antiepileptic drugs (AEDs) are anticonvulsants. Traditional AEDs, while generally successful in controlling seizures, often have adverse effects, and therefore new AEDs are in demand. One recently identified AED is rufinamide (**4**). Rufinamide, which likely blocks calcium channels, has been approved for the treatment of Lennox–Gaustaut syndrome, a severe form of childhood epilepsy.[1–3]

Several syntheses of rufinamide have been reported.[4–7] All routes begin with 2,6-difluorobenzyl azide (**1**), which may be prepared by reacting the corresponding, commercially available chloride with sodium azide.[4] The various syntheses of rufinamide differ by the dipolarophile that undergoes cycloaddition with azide **1** to form the triazole ring. The three different reported dipolarophiles are ethyl propiolate,[4] propiolic acid[5,6] and 2-chloroacrylonitrile (**2**).[6,7] The nitrile route is shown in Scheme 1.

Comparisons of the literature routes to rufinamide are difficult because of varying degrees of experimental disclosure. Regardless, the 2-chloroacrylonitrile route appears to be the best. It affords rufinamide in a high overall yield of 85%, requires only two synthetic steps and has the least expensive[8] dipolarophile of the three pathways. The 2-chloroacrylonitrile route is also the only method that has been implemented as a one-pot process. The route, however, is not without problems. 2-Chloroacrylonitrile is characterized as both highly toxic and flammable. The nitrile route also generates a considerable amount of waste with an estimated overall *E*-factor of 20.2.[9]

Given the shortcomings of the literature syntheses, we sought to adapt our previously reported azide-enol ether cycloaddition methodology to prepare rufinamide.[10] Our goal was to develop a simple, scalable synthesis that is more efficient, uses safer reagents and generates less waste than the established nitrile-based method.

2. Results and discussion

We initially envisioned two similar routes to rufinamide by azide-enol ether cycloadditions (Scheme 2). Both 3-methoxyacrylonitrile (**6**) and methyl 3-methoxyacrylate (**7**) should react with azide **1** to afford triazoles (**3** and **5**) that can be converted to rufinamide. In related research, we have observed 3-methoxyacrylonitrile (**6**) to react with azides and afford a mixture of regioisomeric products.[10] Therefore, enol ether **7**, which undergoes cycloadditions with azides with very high regioselectivity, was selected for the rufinamide synthesis.

The synthetic route to rufinamide begins with the cycloaddition of azide **1** with enol ether **7** (Scheme 3). The preliminary reaction conditions were determined on a 5-g reaction scale of azide **1**. The cycloaddition is performed without solvent at approximately 135 °C and complete within 28 h with a slight excess of the enol ether. Upon completion, cooling the reaction mixture to room temperature affords a solid product of high purity. Although azides and

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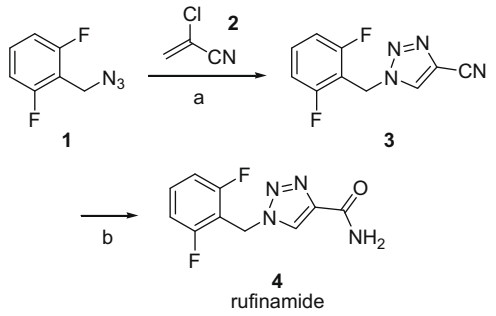
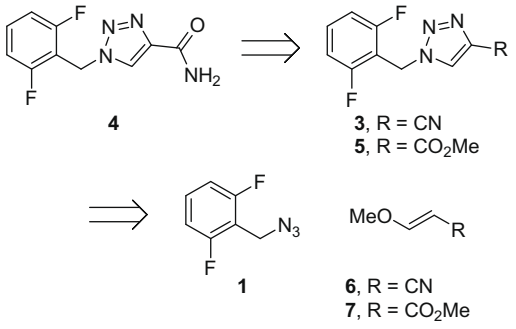


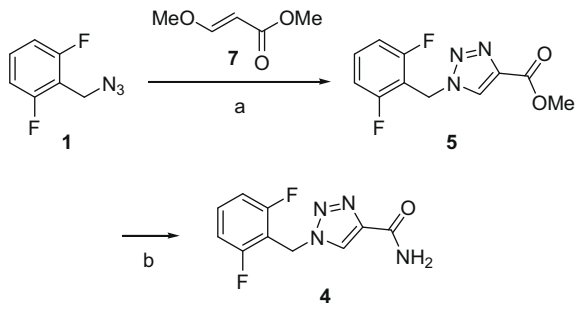
Scheme 1. Synthesis of rufinamide from nitrile **2**. Reagents and conditions: (a) 80 °C, 24 h, 86%; (b) aq NaOH, 95 °C, 1.5 h, 99%.

alkynes react readily with little heating, alkenes are less reactive as dipolarophiles.[11] The exclusion of solvent is therefore necessary to increase reagent concentrations and minimize the reaction time. The second step, ammonolysis of ester **5**, proceeds smoothly in 14 equiv of methanolic ammonia (7 M). Ester **5** slowly dissolves into the solvent while, simultaneously, the newly formed product precipitates from the reaction mixture. Clean rufinamide is isolated by filtration in an overall yield of 79% over two steps when performed on a 5-g scale. The use of enol ether **7** is an improvement over nitrile **2** (Scheme 1). Enol ether **7** costs 30% less than nitrile **2**.[12] Enol ether **7**, listed only as an irritant on its MSDS, is also less toxic than nitrile **2**.

The synthesis contains few variables for optimization. Most of the waste in the synthesis is generated in the second step with the large excess of ammonia. Reduction in the volume of methanolic ammonia unfortunately lengthened the reaction time. In a 10-g batch limited to 6 equiv of ammonia, the ammonolysis required 6 days for completion. Because ester **5** is only sparingly soluble in methanol, reducing the solvent volume also reduces the amount



Scheme 2. Possible retrosyntheses of rufinamide (**4**).



Scheme 3. Two-pot and one-pot syntheses of rufinamide (**4**). Reagents and conditions for 5-g scale, two-pot synthesis: (a) no solvent, 135 °C, 28 h, 85%; (b) NH_3 in MeOH, 25 °C, 18 h, 93%. Reagents and conditions for 35-g scale, one-pot synthesis: (a) no solvent, 135 °C, 24 h; (b) NH_3 in MeOH, 25 °C, 72 h, 89% over two steps.

of ester that is available for reaction. Furthermore, the reaction mixture becomes overly thick with product and unreacted starting material if too little methanol is present. The only significant improvement over the initial synthesis is adaptation of the synthesis to a one-pot method. The second step can be performed by addition of the ammonia solution to the cooled cycloadduct.

The optimized synthesis has been completed on a 35-g scale of azide **1** as a one-pot process (Scheme 3). On this scale, the cycloaddition was performed in a covered beaker and completed within 24 h. An excess of methanolic ammonia was added to the solid cycloadduct (**5**), and the vessel was again loosely covered to minimize loss of ammonia. After 72 h rufinamide (**4**) was isolated by filtration in an 89% overall yield from azide **1**. Concentration of the filtrate afforded an additional 3% of product as well as 3% recovered ester **5**. The *E*-factor of the entire process was 14.6.

Safety is always a concern in a laboratory environment, and azides are indeed reactive functional groups. Studies on the thermal stability of azide **1** have not been performed.[13] Based upon our previous research,[10] we have found that alkyl azides can be used in thermal cycloadditions with enol ethers without incident. Regardless, all reactions of azides should be performed with appropriate precautions, including exclusion of metal salts and acids, use of blast shields and avoiding alkyl azides that contain alkyne functionality.[14]

In conclusion, we have developed a two-step, one-pot process for the production of rufinamide through an azide-enol ether cycloaddition. In comparison to other reported methods, the new route has a higher overall yield and generates less waste. Finally, the dipolarophile of the new route is less toxic and less expensive than those used in alternative syntheses.

3. Experimental procedures

3.1. Two-pot, 5-g scale synthesis of 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxamide (4)

Crude 2,6-difluorobenzyl azide[4] (**1**) (5.00 g, 29.6 mmol) and methyl 3-methoxyacrylate (**7**) (3.78 g, 32.6 mmol) were heated neat to 135 °C. At 2 h and 18 h additional aliquots of **7** (0.216 g) were added. After 28 h the mixture was cooled to rt. The crude product was recrystallized from MeOH to afford 6.40 g (85%) of methyl 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxylate (**5**) as a white solid. Ester **5** (6.40 g, 25.3 mmol) was suspended in methanolic NH_3 (50 mL, 350 mmol, 7 M). The reaction mixture was stirred at 25 °C, the consumption of ester **5** was followed by GC. After 18 h water (10 mL) was added and the thick reaction mixture was cooled to 0 °C. Filtration of the reaction mixture afforded 5.62 g (93%) of the title compound as a white solid. Data for **5**: mp 135–137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.37 (tt, J = 8.4, 6.6 Hz, 1H), 6.99–6.91 (m, 2H), 5.65 (s, 2H), 3.89 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 161.4 (dd, $^1J_{CF}$ = 250 Hz, $^3J_{CF}$ = 6.7 Hz), 161.1, 140.2, 132.0 (t, $^3J_{CF}$ = 10.3 Hz), 127.6, 112.0 (m), 110.1 (t, $^2J_{CF}$ = 18.7 Hz), 52.2, 41.8 (t, $^3J_{CF}$ = 3.8 Hz); ^{19}F (376 MHz, $CDCl_3$) δ 113.9 (s, 2F). Data for **4**: mp 240–241 °C (lit[4] 236–238 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 7.88 (br s, 1H), 7.57–7.48 (m, 2H), 7.22–7.15 (m, 2H), 5.73 (s, 2H); ^{13}C (100 MHz, DMSO-d_6) δ 161.9, 161.4 (dd, $^1J_{CF}$ = 250 Hz, $^3J_{CF}$ = 7.3 Hz), 143.4, 132.4 (t, $^3J_{CF}$ = 10.3 Hz), 127.4, 112.5 (m), 111.6 (t, $^2J_{CF}$ = 19.1 Hz), 41.8 (t, $^3J_{CF}$ = 3.8 Hz); ^{19}F (376 MHz, DMSO-d_6) δ 114.4 (s, 2F).

3.2. One-pot, 35-g scale synthesis of 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxamide (4)

2,6-Difluorobenzyl azide[4] (**1**) (35.4 g, 209 mmol) and methyl 3-methoxyacrylate (**7**) (26.7 g, 229 mmol) were heated neat to

135 °C. At 18 h an additional aliquot of **7** (0.50 g) was added. After 24 h the mixture was cooled to rt. The crude product (**5**) was finely divided in the reaction flask and suspended in methanolic NH_3 (400 mL, 2.80 mol, 7 M). The reaction mixture was stirred at 25 °C for 24 h, after which additional MeOH (100 mL) was added to facilitate stirring. After 72 h the mixture was cooled to 0 °C and filtered. The resulting solid was washed with ice cold MeOH (300 mL) to afford 44.4 g (89%) of the title compound as a white solid. Concentration of the filtrate afforded 2.8 g of a 1:1 mixture of recovered starting material (**5**) (3%) and product (3%).

Acknowledgement

We thank Professor William R. Dolbier, Jr. of the University of Florida at Gainesville for assistance in interpreting the carbon–fluorine coupling in the ^{13}C NMR spectra of compounds **4** and **5**.

Supplementary data

Supplementary data (*E*-value calculations and NMR spectra for **4** and **5**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.060.

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