Preparation of 4-Azido-2,6-diflurophenol Acetate, a Click Reagent

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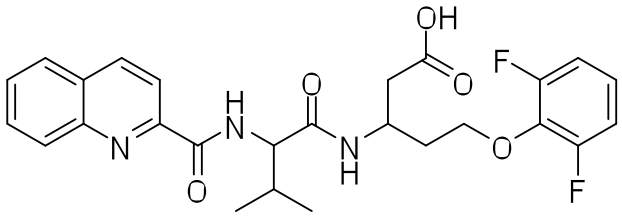
Abstract: The title compound was prepared from 2,6-difluorophenol in four steps. Acetylation, followed by nitration, reduction to the amine and diazotization/azide formation proceeded in the expected fashion.

A copper-catalyzed Huisgen cyclization between the compound and phenylacetylene was carried out as a model and the triazole isolated. The propargyl ester of naproxen was prepared (naproxen/propargyl alcohol/carbodiimide) and the subsequent click reaction carried out. It is expected that this strategy will afford access to materials with dual biological activity.

Keywords: click chemistry, naproxen, 2,6-difluorophenol

Introduction:

The 2,6-difluorophenol moiety has been an interesting building block in the preparation of various inhibitor molecules and is often used as a bioisostere for a carboxylic acid. [1,2] We were initially drawn to this area by the structure of quinolyl-vayl-O-methylaspartyl-[2,6-difluorphenoxy]-methylketone: Q-VD-OPh (**1**).[3] This molecule is a synthetic capsase inhibitor that is capable of crossing the blood brain barrier.



1

The inhibition of capsase has promising applications in the prevention of apoptosis. Since the damages caused by stroke relate to both apoptosis and inflammation, we undertook a study to determine whether the difluorphenyl group was amenable to azide-alkyne click chemistry of the Huisgen type, with the specific goal of preparing a Q-VD-OPh analog with an NSAID attached to the aromatic ring. We report herein our progress in the area.

Experimental:

2,6-difluoro-4-nitrophenol
Nitric Acid (300 mg, 4.7 mmol) was added dropwise at 5°C to a stirred solution of 2,6-difluorophenol (500 mg, 3.8 mmol) in acetic acid (2.5 mL). After addition was complete the mixture was allowed to warm to ambient temperature, stirred for 1 h and poured into ice-water (2 mL). The resulting solution was concentrated under reduced pressure to about 1 mL and the product was extracted into dichlormethane (5x, 25 mL). The combined extracts were washed with water (2x), dried with $MgSO_4$ and the solvent was removed *in vacuo*. The residual oil was heated under reflux with isooctane (30 mL) for 15 minutes, the solution decanted from an insoluble residue and cooled in ice-water. The resulting yellow solid was collected by filtration and dried *in vaco* to give 2,6-difluoro-4-nitrophenol (376 mg, 56%). mp 100-102°C. ^{1}HNMR (500 MHz, $CDCl_3$): δ (ppm) 5.95 (s, 1H, OH), 7.82 (m, 2H, Ar-H).

2,6-difluoro-4-nitrophenyl acetate
2,6-difluoro-4-nitrophenol (350 mg, 2.0 mmol) was stirred with sodium carbonate (870 mg, 8.3 mmol) and acetic anhydride (700 mg, 6.8 mmol) in a round bottom flask in an ice bath. The resulting reaction mixture was allowed to reach room temperature and stirred overnight. Saturated sodium bicarbonate was added and the reaction stirred for 1 h. The reaction slurry was extracted with chloroform and washed with water. The organic layer was dried and concentrated to yield a brown solid (318 mg, 73%). ^{1}HNMR: 2.44 (s, CH_3), 7.95 (d, Ar-H, J= 6.6). IR 3101, 2962, 1785, 1496, 1168 cm^{-1}.

4-amino-2,6-difluorophenyl acetate
A suspension of 2,6-difluoro-4-nitrophenyl acetate (250 mg, 1.2 mmol) and 10% Pt-C (50 mg) in methanol (5 mL) was stirred with ammonium formate (115 mg, 1.8 mmol) at room temperature. After completion of the reduction (monitored by t.l.c.), the catalyst was filtered through a celite pad and flushed with methanol. The combined washings and filtrate were evaporated *in vacuo.* The residue was taken up in chloroform and washed with saturated NaCl. The organic layer on evaporation yielded a brown solid (48%). ^{1}HNMR: 2.15 (s, CH_3), 6.48 (d, NH_2, J= 8.1), (7.89 (d, Ar-H, J=7.8). IR: 3327, 1764, 1616, 1516 cm^{-1}.

4-azido-2,6-difluorophenyl acetate
In a small vial, 4-amino-2,6-difluorophenyl acetate (50 mg, 0.28 mmol) and sodium nitrite (100 mg, 1.45 mmol) was dissolved in 0.1M HCl at 0°C for 15 minutes, at which point sodium azide (100 mg, 1.54 mmol) was added and the mixture allowed to stir for one hour. The mixture was extracted with ethyl acetate, dried (MgSO4) and concentrated *in vacuo* to afford a brown solid (21% yield). ^{1}HNMR: 2.27 (s, CH_3), 6.53 (d, Ar-H, J= 11.1) IR: 3378, 2917,2114, 1764, 1646, 1608, 1516 cm^{-1}.

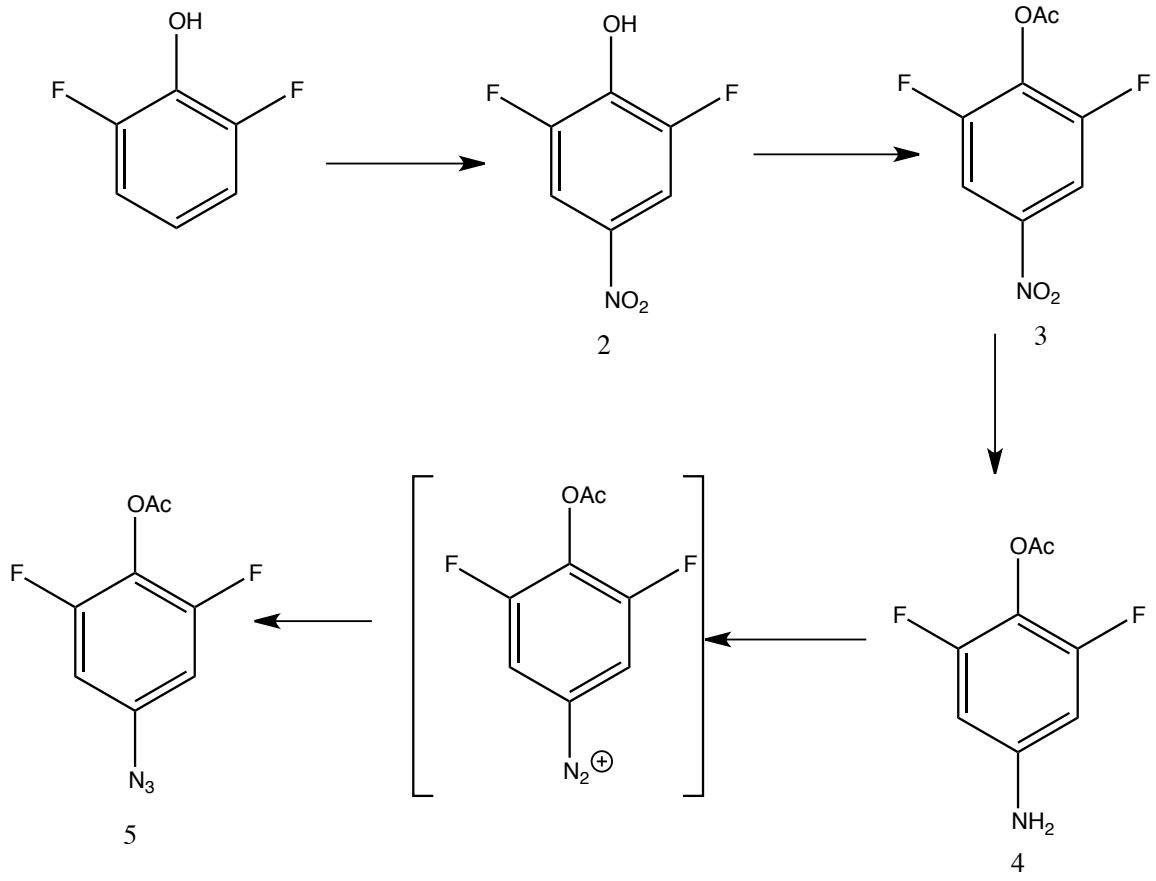
Propargyl naproxen ester
Naproxen (2.30 g, 10 mmol) was dissolved in CH_2Cl_2 (25mL) along with *N,N*-dicyclohexylcarbodiimide (2.06 g, 10 mmol). The reaction was stirred for 15 minutes, propargyl alcohol (0.96 mL, 10 mmol) was added and stirred overnight. The reaction was filtered, extracted with CH_2Cl_2 (25 mL) and washed with water, dilute HCl (0.1M), saturated sodium carbonate and water again, dried over $MgSO_4$, filtered and concentrated to yield 2.214 g/mol (82%) of a white solid. IR: 3255, 2128, 1728, 1169, 2939 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$): δ (ppm) = 1.44 (d, 3H, CH_3), 1.59 (t,1H,-CH_2), 3.72 (s, 3H, OCH_3), 4.55 (q,CH) (7.16-7.78 (m, 6H). ^{1}HNMR was in agreement with published data.

(1-(4-acetoxy-2,6-difluorophenyl)-1H-1,2,3-triazol-4-yl)methyl 2-(7-methoxynaphthalen-2-yl)propanoate. 4-azido-2,6-difluorophenyl acetate (100 mg, 0.50 mmol) and propargyl naproxen ester (126 mg, 0.50 mmol) were dissolved in tert-butanol (5 mL). Ascorbic acid (8.3 mg, 0.05 mmol) and copper(II) sulfate (12 mg, 0.05 mmol) was dissolved in water (3 mL) and the two solutions were added together to stir overnight with monitoring by TLC. The reaction mixture was diluted with water and cooled in ice for 10 minutes, and the brown/black precipate was collected by filtration. The precipate was extracted with chloroform, washed with cold water (2x), dried with MgSO4 and concentrated. The residue was chromatographed on silica gel with 100% ethyl acetate to afford a brown solid in 14% yield. ^{1}HNMR (500 MHz, $CDCl_3$): δ (ppm) = 1.61 (d, 3H, CH_3), 1.72 (t,1H,-CH_2), 2.15 (s, CH_3), 4.04 (s, 3H, OCH_3), 4.62 (q,CH), 7.16-7.78 (m, 6H), 8.20 (d, 1H, CH-N).

Results and Discussion:

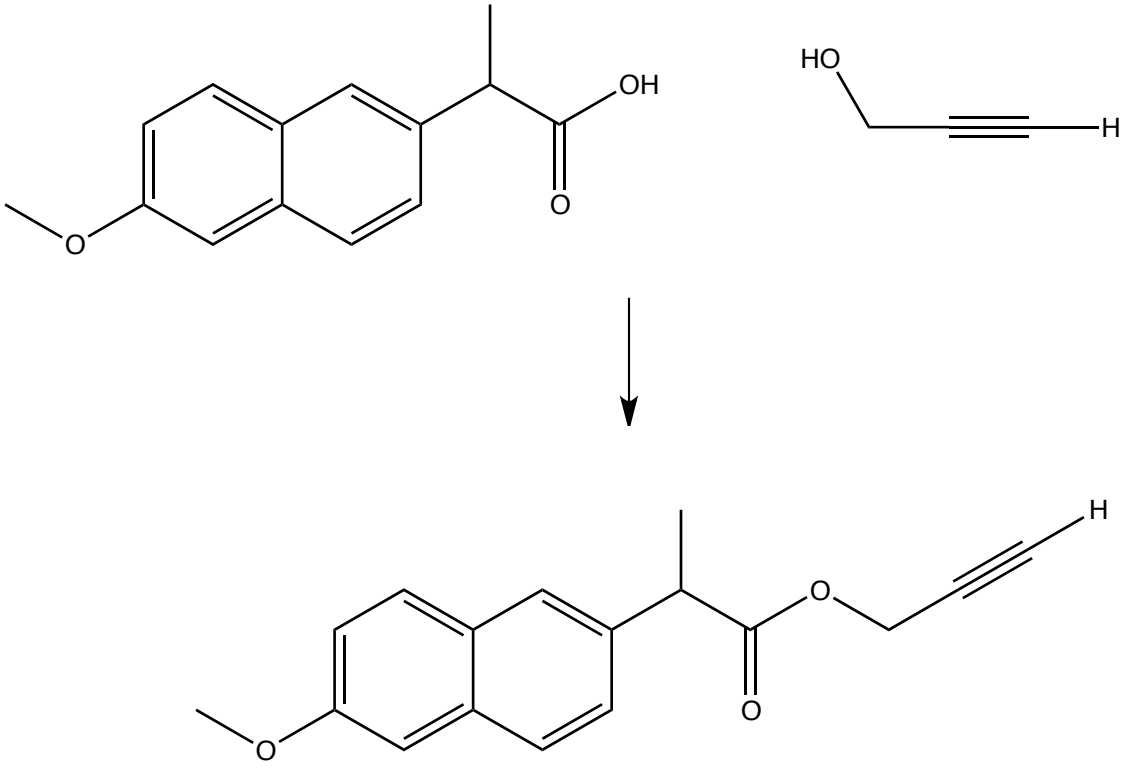
The preparation of 4-azido-2,6-difluorophenol acetate proceeded within expected parameters (Scheme 1). Nitration of 2,6-difluorophenol using nitric acid in acetic acid afforded the nitro compound 2 in 56% yield[4]. Acetylation to 3 in acetic anhydride proceeded in 73% yield. Subsequent reduction (ammonium formate/Pt/C) gave the aniline 4 in 48% yield[5]. Diazotization followed by formation of the azide 5 was carried out in a one-pot reaction using sodium nitrite/HCl and sodium azide and proceeded in 21% yield[6].

While the nitro compound is known and there is similar chemistry up to the aniline reported on the analogous anisole, the experimental protocols are slightly different. To our knowledge, the azido phenol acetate is not a known compound.



Scheme 1. Preparation of 4-azido-2,6-difluorophenol acetate.

Upon preparation of the azide a simple model was chosen, the reaction of phenylacetyelene and 5 (Scheme 2). While this reaction appeared to yield the product, it was not pursued, moving instead to a reaction with an NSAID derivative. Ester 6 was prepared by the reaction of propargyl alcohol with naproxen using DCC as the coupling reagent (82%)[7]. The ester is a known compound, though this is a new preparation. To our knowledge, the ester has never been reported in a click reaction.



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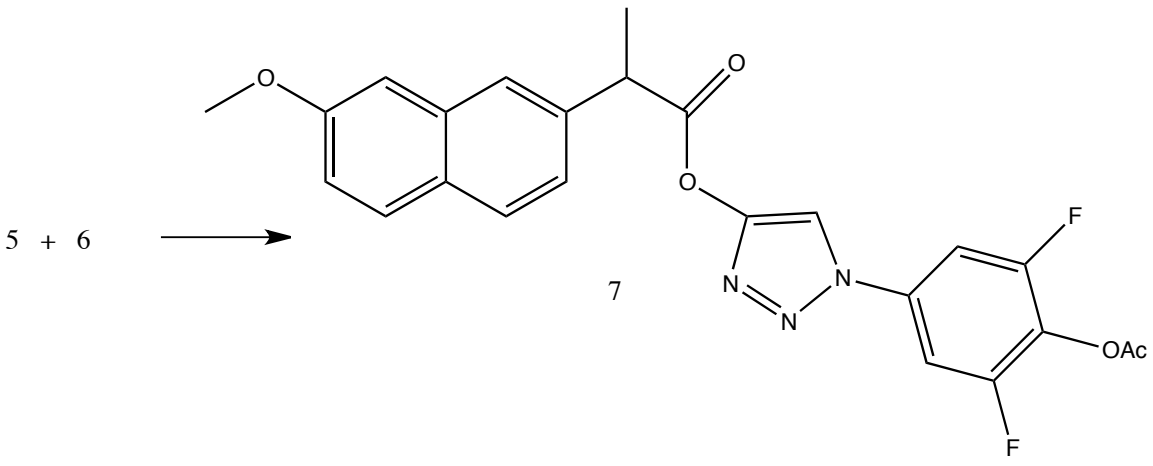
Scheme 2. Esterification of Naproxen

With the two components in hand the click reaction between compounds 5 and 6 was carried out under conditions of copper catalysis., yielding the desired product.



7

Conclusion:

The click reaction for the coupling of 4-azido-2,5-difluorophenol acetate and naproxen propargyl ester proceeds in the anticipated fashion. Future plans center about the coupling with other NSAIDs and attachement to Q-VD.

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References:

1. Qiu, J., Stevenson, S. H., O'Beirne, M. J. , and Silverman, R. B., *J. Med. Chem.* **1999,** *42,* 329-332.
2. Nicolaou, I., Zika, C., and Demopoulos, V. J., *J. Med. Chem.* **2004,** *47,* 2706-2709.
3. Callus, B.A.; Vaux, D.L. *Cell Death and Differentiation*, **2007**, *14*, 73-78.
4. Bartolini, W., Cali, B. M., Chen, B., Chien, Y.-T., Currie, M. G., Milne, G. T., Pearson, J. P., Talley, J. J., Zimmerman, C., US 20050234244
5. Gowda, D. C.; Mahesh, B. *Synthetic Communications*, **2000**, *30*, 20, 3639-3644.
6. J. C. Kauer, R. A. Carboni, *J. Amer. Chem. Soc*. **1967**, *89*, 2633 – 2637.
7. Zhao, Q.-Y., Zhang, W.-Q.;, Zhang, Y.-H., Hu, B., Yin, Y.-Q., Xia, C.-G., *Organometallics*, **2004**, *23*(4), 817-822.
8. Himo, F., Lovell,T., Hilgraf,R., Rostovtsev,V. V., Noodleman,L., Sharpless, K. B., and Fokin, V. V., *J. Amer. Chem. Soc.*, **2005**, *127*, 210-216.