Honors Cup Synthetic Proposal

Section: 250.2
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Title: A Three-step Synthesis of Naproxen

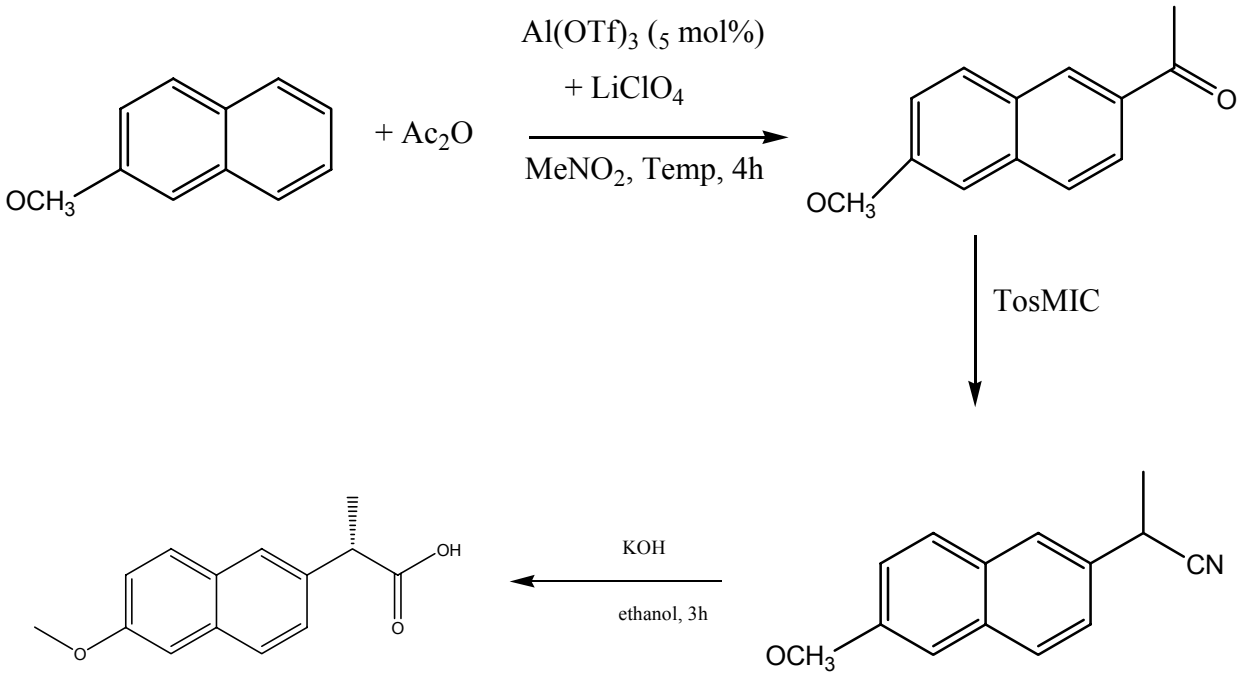
Introduction

Recent Naproxen information has revealed that this drug may cause an increased risk of cardiovascular side effects in patients taking even the over the counter strength of this pain medication. This naproxen information was announced publicly by the FDA in December 2004 after clinical trials revealed this potential risk. The National Institute of Health initiated a drug trial in 2001 to test the effectiveness of some medications in preventing Alzheimer's disease. This study was halted after naproxen information revealed that the trial participants taking naproxen were twice as likely to suffer from heart attack or stroke as patients in the control group.

Source: http://www.adrugrecall.com/naproxen/information.html

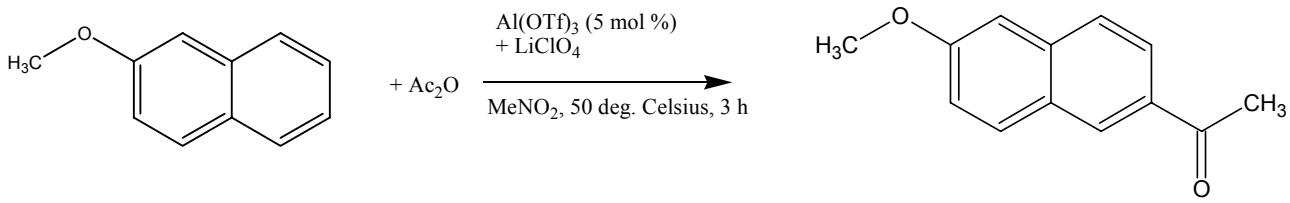
As the above abstract shows, Naproxen has been subject to a firestorm of criticism in recent months. Although we aren't attempting to investigate its biological effects, we think it synthesizing a molecule as controversial as this would not only be fun, but also lend a sense of accomplishment from the knowledge that we can make a (previously) marketable prescription drug in class.

Overall synthetic reaction scheme



Step 1

Synthetic transformation 1



Experimental 1

To a mixture of 2-methoxynapthalene (1.059 g, 6.695 mmol) and $LiClO_4$ (4.28 g, 40.3 mmol) in $MeNO_2$ (10 mL), $Al(OTf)_3$ (0.237 g, 0.5 mmol, 5mol%) was added. Acetic anhydride (7.17 g, 70.2 mmol) was slowly added at 50^oC for 5 minutes, after which the reaction was stirred for 3 hrs. After the mixture was poured into saturated aqueous $NaHCO_3$ (50 mL), the mixture was extracted with Et_2O (100 mL x 2), and the combined organic layer was washed with H_2O (50mL x 2). The organic extract was dried with anhydrous Na_2SO_4, filtered, and evaporated to give a crude oil. This crude product was treated with activated charcoal in AcOEt, and then filtered. The solvent was removed and the residue was recrystallized from heptane to afford 2-acetyl-6-methoxynapthalene (0.9 g, 4.49 mmol, 75%).

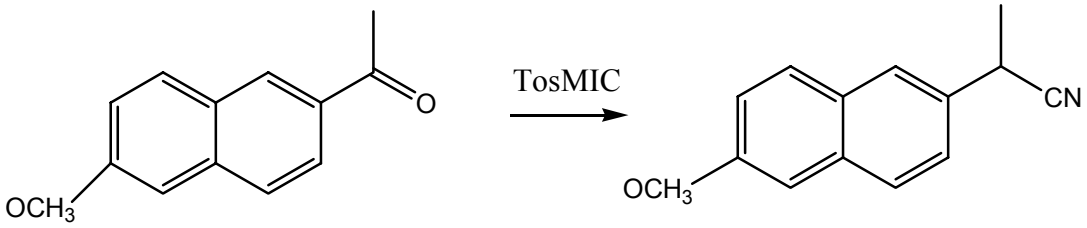
The expected yield was adjusted from 83% to 75% to account for error, and scaled upward by a factor of 5.7. Original yield was 83% (1.11 g). Time was decreased from 5 hrs. to 3 to account for time constraints of the lab period. According to Fig. 1 of the journal article (see article), the product is sufficiently reacted at 3 hrs. for the purposes of this synthesis.

Expected yield: 75% ; 1000 mg or 1.0 g

Safety, disposal and green issues 1:

There are no specific safety issues in Step One of this synthesis. Regular safety procedures should be followed in the laboratory, and chemical residue should be disposed of in proper waste areas.

Synthetic transformation 2



Experimental 2

A solution of 97% *t*-BuOK (700 mg, 6.0 mmol) in hot t-butanol (3.1 ml) was carefully added to a well mixed solution, cooled to -20°C, of 2-acetyl-6-methoxynaphthalene (670 mg, 3.35 mmol) and TosMIC (670 mg, 3.35 mmol) in dimethoxyethane (12 ml), which was in a 50-ml round bottom flask, keeping the temperature below 0°C. The flask was capped with a septum to hold the temperature steady, and the mixture was stirred at -20°C for 15 minutes and then at room temperature for 3.0 h. After concentration, the mixture was treated with 67 ml of water and extracted with chloroform (3x 67 ml) using a separatory funnel.

The extracts were collected, washed with water, and dried. The solvent was removed by rotary evaporation, leaving the product, which was purified by silica gel column chromatography using a 1:1 chloroform-petroleum ether eluent.

The expected yield was changed to 70% from the 86%-89% range to account for experimental error. Also, since the experimental provides for 470 mg and our target yield is 630 mg, all substances were scaled up by a factor of 630/470, or about 1.34 times their amounts in the experiment. Also, the time of stirring at room temperature was reduced to 3.0 h instead of 3.5 h, to provide for the limitations of laboratory time.

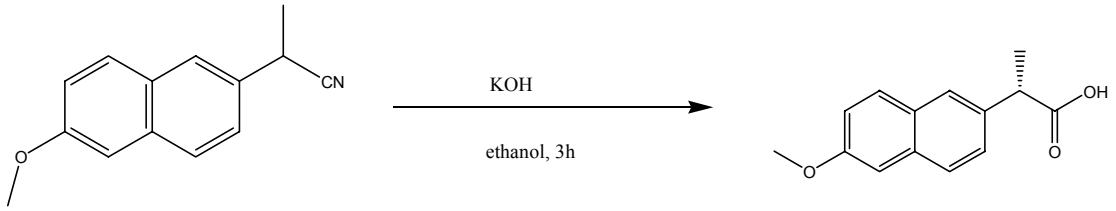
Expected yield: 70% 0.630g

Safety, disposal and green issues 2:

There are no specific safety issues unique to this reaction. However, as in all cases, all reasonable precautions should be taken (wear gloves and goggles, perform the reaction under the hoods, etc.).

Step 3

Synthetic transformation 3



Experimental 3

A mixture of the product of step 2(630 mg, 3.0 mmol) and 1.0N potassium hydroxide (15 mL, 15 mmol) in ethanol (3 mL) was refluxed for 3h. 30 mL water and 10 mL 1N HCl were added, and the resulting precipitate was extracted with ethyl acetate (3x20mL). The organic layers were collected, washed with brine (3x40mL) and dried. The solvent was evaporated and the resulting product was recrystallized from toluene (0.5125 g, 75%).

The expected yield was adjusted from 90% to 75% to account for error, and scaled upward by a factor of 3. Original yield was 90% (205 mg). In addition, to make this step more budget-friendly, the KOH concentration was changed from 10N to 1N, and the amount needed was scaled accordingly. The time was also reduced from 5h to 3 to account for the time constraints of the lab period.

Expected yield: 75% 0.5125 g

Safety, disposal and green issues 3:

There are no specific safety issues with this step, save for the precautions normally taken when working with bases such as KOH. This reaction, as most others, should be done under the hood, wearing gloves and goggles and taking all reasonable precautions.

Overall budget

Chemical	Supplier	Cost	Amt. Needed	Total
2-methoxynaphthalene	Aldrich	$12.80/100g	1.059g	$0.135
$LiClO_4$	Aldrich	$151.40/500g	4.28 g	$1.30
$Al(OTf)_3$	Aldrich	$249/50g	0.237g	$1.18
Acetic Anhydride	Aldrich	$44.10/L	6.639 mL	$0.293
97% *t*-BuOK	Aldrich	$115.90/500g	0.7g	$0.162
t-butanol	Aldrich	$48.40/2L	3.1 mL	$0.075
TosMIC	Aldrich	$101.50/25g	0.670 g	$2.72
1.0 N KOH	Aldrich	$23.10/2L	0.015 L	$0.3465

Total costs per synthesis: $6.2115

References (include at least two different sources for your experimentals):

http://www.adrugrecall.com/naproxen/information.html

Kobayashi, S.; Komoto, I. *Tetrahedron* **2000**, *56,* 6463-5

Santo, R.; Costi, R.; Massa, S.; Artico, M. *Synthetic Communications* **1995** *25*, 787-93.