Honors Cup Synthetic Proposal

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

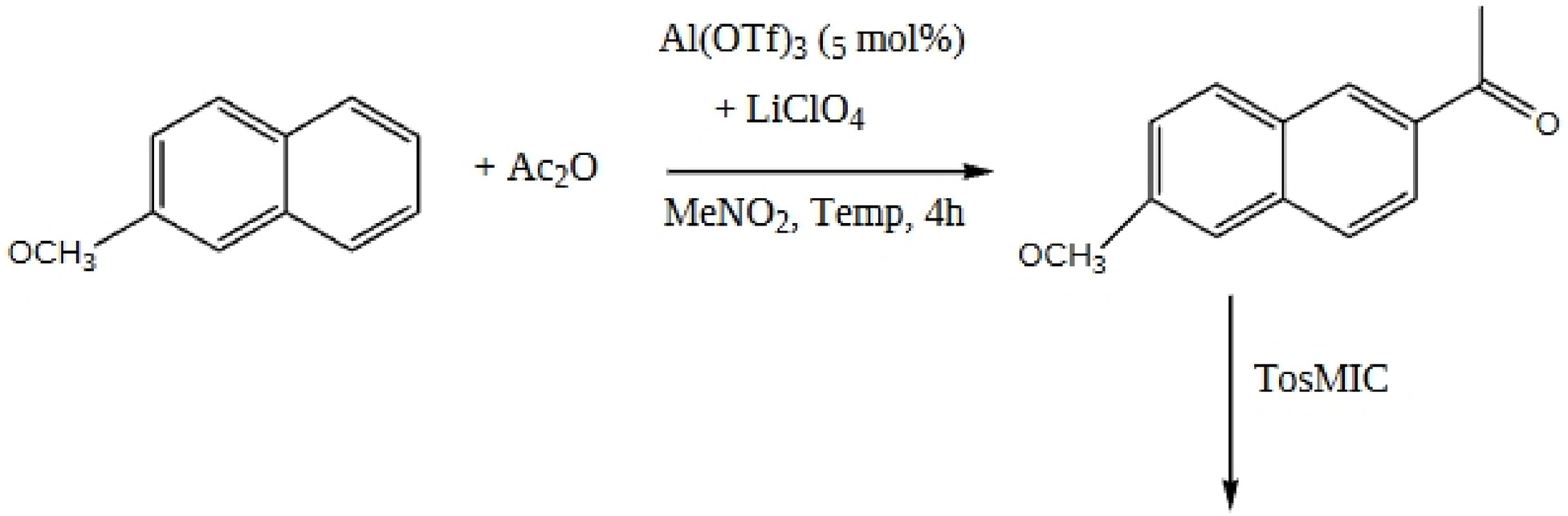
Introduction

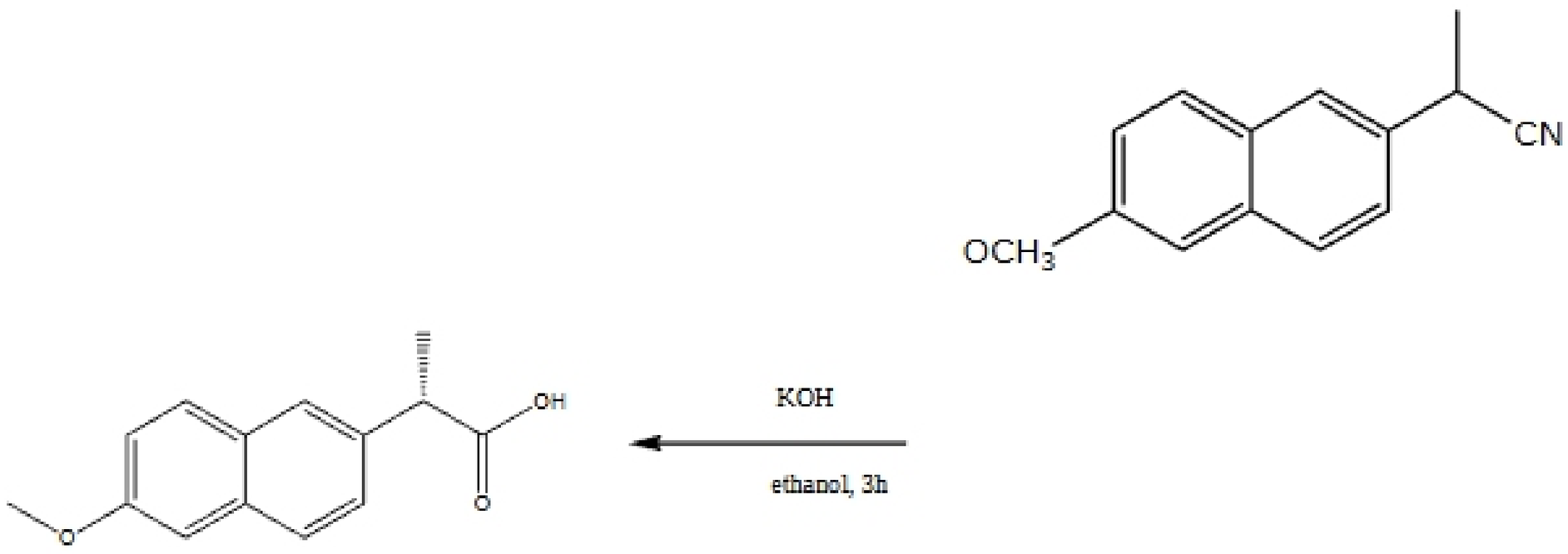
Recent Naproxen information has revealed that this drug may cause an increased risk of cardiovascular side effects in patients taking even the over the counter strength of this pain medication. This naproxen information was announced publicly by the FDA in December 2004 after clinical trials revealed 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.

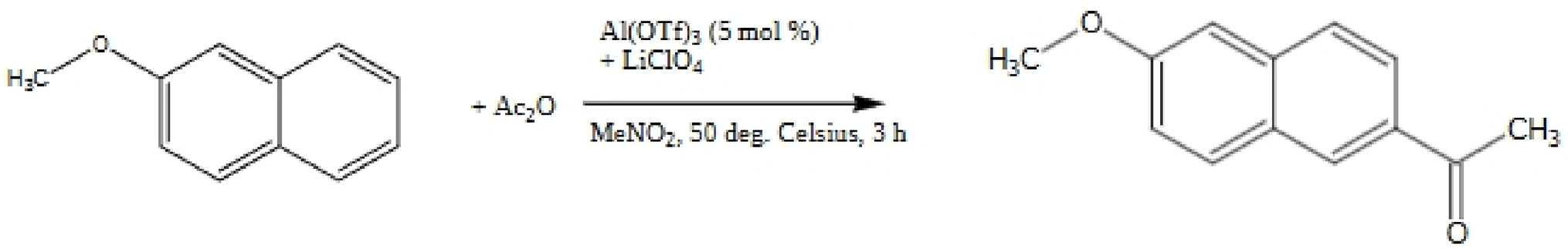
Overall synthetic reaction scheme





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° C 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.