UCLA Chemistry 144 Organic Synthesis

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Experiment 1 Chemoselective Enone Reduction and Urethane Synthesis

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Abstract: The chemoselective 1,2 reduction of an enone to an α,β-unsaturated alcohol is investigated with $NaBH_4$ in methanol. Yields are high, conditions are mild, and reaction time is fairly fast which makes this a useful reagent for organic synthesis. A unique urethane is then synthesized by employing the alcohol of the reduced enone as an intermediate in order to demonstrate the usefulness of $NaBH_4$ as chemoselective reducing agent.

Introduction:

Synthetic routes to urethanes, or carbamates, are of interest to study since they have a broad range of applicability. Natural occurrences of carbamates such as RuBisCO, the key CO_2 fixing enzyme in plants, have potential for exploiting its CO_2 fixing ability to offsetting the effects of global warming.[1] Urethanes are also useful commercially since they are the base of several insecticides as well as polymers are made with a wide range of properties for various polyurethane materials.

The reaction scheme (figure 1) starts with a chemoselective reduction to an alcohol (2) and subsequent spontaneous reaction with phenylisocyanate (3) to form a urethane (4). Sodium borohydride is the reducing agent of choice since it works well in mild conditions to reduce ketones to alcohols in high yield. $NaBH_4$ does not reduce alkenes or benzene rings, so it is a convenient reagent to selectively reduce the trans-4-phenyl-3-buten-2-one (1).[2] $LiAlH_4$ could be used instead although it is more prone to conjugate reduction, and it reacts violently with methanol and water.[3] Isocyanates react spontaneously with alcohols to form urethanes,[4] so the synthesized α,β-unsaturated alcohol (2) was simply stirred neat with phenylisocyanate (3) to yield urethane (4).

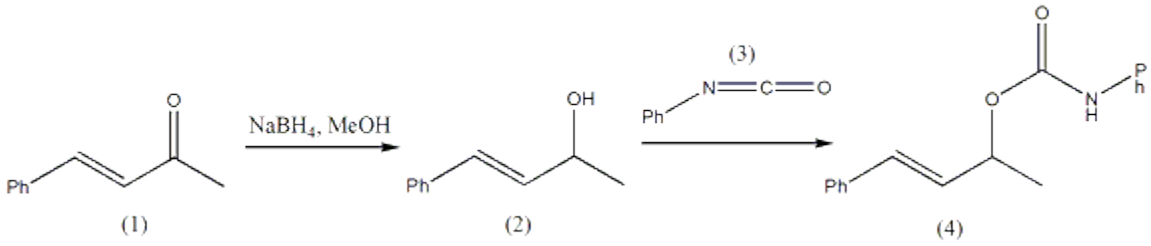

Figure 1: Reaction Scheme

Discussion:

The first step involves reduction of the enone (1) to α,β-unsaturated alcohol (2) by the reducing agent $NaBH_4$ in methanol, though other solvents such as THF and ethanol work well.[5] The reaction occurs by hydride attachment onto the carbonyl and subsequent binding and hydride transfer from BH_3 to the ketone's oxygen. The reaction required more $NaBH_4$ and a significantly longer reaction time than

specified.[3] Conditions of methanol-THF solvent at 0°C report reaction times as low as 20 minutes, so these conditions could be emulated to see if reaction time is reduced.[2] Slow reaction time could also be attributed to not using dry methanol, as water reacts exothermically with $NaBH_4$ evolving H_2 gas.[5] Yields of 89% exceeded published values of 86%.[2] Comparison of FT-IR spectroscopy of the enone (1) to the alcohol (2) support successful reduction with appearance of broad 3333cm^{-1} OH peak and elimination of 1667cm^{-1} C=O peak. ^1H NMR and ^{13}C NMR confirms the identity of the alcohol (figure 2). Additional comparison of ^1H NMR and FT-IR to published data[6] further supports successful synthesis.

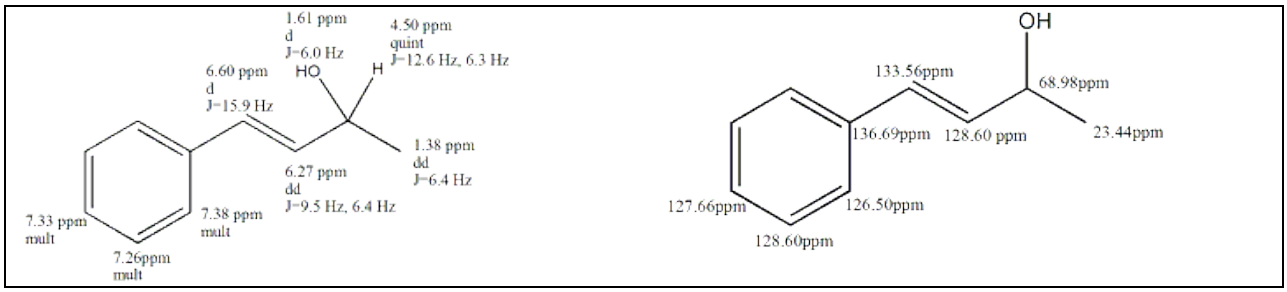

Figure 2: Alcohol (2) NMR Analysis

The next step involved spontaneous reaction of the alcohol (2) with phenylisocyanate (3) which occurred at 70°C to create a urethane (4). Though the reaction was carried out neat, the use of different solvents and their resulting kinetic effects have been studied extensively.[4] The reaction involves an autocatalysis mechanism in which the alcohol and isocyanate form a complex which then reacts with a second alcohol molecule to form the urethane and free alcohol.[4] FT-IR suggests the reaction occurred as predicted with disappearance of hydroxyl peaks and appearance of 3342 cm^{-1} (amine) and 1700 cm^{-1} (carbonyl) peaks. The proton NMR was well accounted (Figure 3), though the carbon NMR was poor with only three sp^2 peaks acquired. Better carbon spectra could be obtained by preparing a more concentrated sample, acquiring more than 32 scans, or processing to pick lower intensity peaks. The isolated compound was 82mg white powder with yield of 37.9%. Yield might have been affected due to a moisture droplet that was observed in the alcohol. Protic solvents have been shown to interact with alcohol's active hydroxyl hydrogen to reduce reactivity, so a protic water droplet would be detrimental to the reaction.[4] The droplet could have been removed prior to starting the reaction by drying with Mg_2SO_4 and filtering again. The procedure could additionally be modified to include a tertiary amine as a catalyst[4], though this would just speed the reaction and would not improve yield since TLC showed that the alcohol was completely reacted. A different approach to purification such as flash chromatography could be considered if the recrystalization in hexane was the source of significant loss.

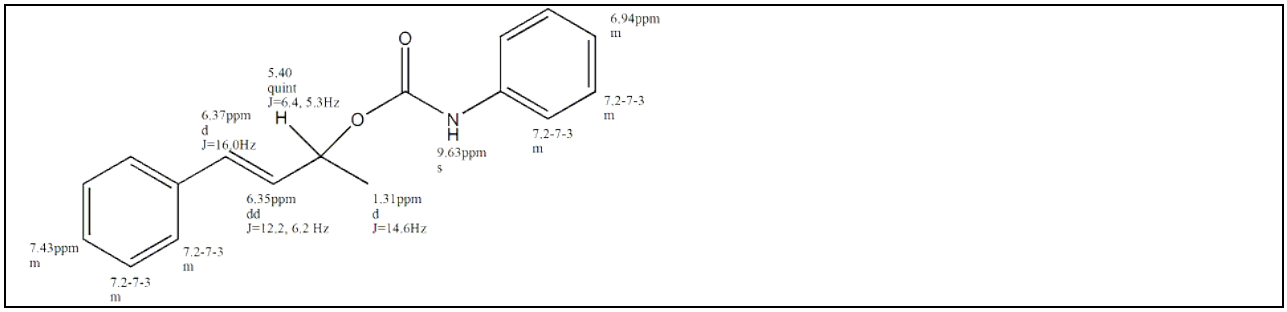

Figure 3: Urethane (4) NMR Analysis

Conclusion and Summary:

The reduction of enone (1) using $NaBH_4$ was highly successful with yields slightly higher than published values and spectra confirming purity. Since the reduction is conveniently a 1,2 reduction of an enone, $CeCl_3$ could be used along with $NaBH_4$ and methanol to further enhance preference of 1,2 reduction up to 100% yield and only 3-5 minute reaction time.[7]

The urethane was successfully synthesized and purified, though yield could be improved with more care removing the residual water droplet in the alcohol (2). The procedure could be modified to use a tertiary amine catalyst at slightly lower temperatures such as 40°C, though this would be experimental and has not been shown to necessarily improve yield. The reaction could also be modified to use an aprotic solvent because it is believed to solvate the phenyl/isocyanate/alcohol complex at the active hydrogen to form an ion-pair which undergoes urethane reaction easier.[4]

Experimental:

trans-4-phenyl-3-buten-2-ol (2) Added 0.1765g (1.2mmol) of trans-4-phenyl-3-buten-2-one (1) to a 25ml round bottom flask under N_2 gas flow. 10ml of methanol was added and mixture was held under ice bath. Added 40mg $NaBH_4$ and reaction was monitored by TLC with 4:1 hexane/EtOAc. Additional 13.5mg $NaBH_4$ at 1hr 30min and then 23mg at 2hr 20min completed full reduction of the enone. Quenched the reaction with 1ml dH_2O. Exracted 3x with 10ml diethylether, washed with 10ml saturated NaCl, and dried with Mg_2SO_4. Filtered, rotavap, and hi-vac for 20 minutes. 160mg (1.1mmol) of colorless liquid to yield the alcohol (2) at 89%. FT-IR v(cm^{-1}) 3333 (b), 3059 (m), 3025 (m) 2970 (s) 2926 (m), 2869 (m), 1598 (w), 1493 (m), 1448 (s), 1367 (m) 1295 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.38 (3H, d, J = 6.4 Hz), 1.61 (1H, d, J = 6.0 Hz), 4.50 (1H, quint, J = 12.6 Hz, 6.3 Hz), 6.27 (1H, dd, J = 9.5 Hz, 6.4 Hz), 6.60 (1 H, d, J = 15.9 Hz), 7.38 (2H, m) 7.26 (2H, m), 7.33 (1H, m). ^{13}C NMR (100mhz, $CDCl_3$) δ (ppm) 137.69, 133.56, 129.43, 128.60, 127.66, 126.47, 69.00, 23.44.

4-phenylbut-3-en-2-yl phenylcarbamate (4) Charged a 250ml round bottom flask with 120mg (0.8 mmol) of alcohol (2) under N_2 gas. Syringed 0.30mL phenylisocyanate (3) (2.8 mmol) and placed in a 70°C water bath. Complete reaction of alcohol was shown by TLC at 40 minutes. Recrystalized with 6mL petroleum ether and vacuum filtered. The white powder was hi-vac for 15 minutes to isolate 82mg (0.3mmol) yielding 38%. mp 85.3-86.4°C. FT-IR v(cm^{-1}) 3342(m), 1700(s), 1596(w), 1524(s), 1442(m) 1328 (w), 1296 (w), 1228 (m); ^{1}H NMR (400 MHz, DMSO) δ (ppm) 1.31 (3H, d, J=14.6 Hz), 5.40 (1H, quint, J=6.4, 5.3 Hz), 6.37 (1H, d, J=16 Hz), 6.94 (1H, m), 7.24 (2H, m), 7.30 (2H, m), 7.43 (1H, m); ^{13}C NMR (100mhz, DMSO) δ (ppm) 129.17, 129.13, 126.90.

References

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Spectra