Increasing the Stability of β-keto functional groups inverts the regioselectivity of β-Ketoacetanilides

Taylor N. Hackel*

Faculty sponsor: Dr. Heather Schneck, Chemistry and Biochemistry

ABSTRACT

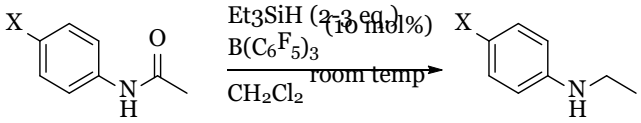
The frustrated Lewis pair tris(pentafluorophenyl)borane with alkyl-substituted silanes has demonstrated efficient, selective, and controlled reduction of a diverse range of functional groups. Its role in the synthetic toolkit as a reductant complements the selectivity of ubiquitous hydride reductants while offering greater flexibility in procedure due to its compatibility with water. The FLP has been shown to exclusively reduce the amide bond of acetanilides possessing carbonyl moieties appended to the para position, whereas the addition of sodium borohydride would exhibit the opposite selectivity. Further, the regioselectivity is reverted when a ketone is positioned βeta to the amide, generating a silyl ether intermediate. McGrath et al. hypothesized the inversion may be justified by a chelating intermediate which activates the previously ignored ketone for reduction[3]. A kinetic study utilizing ^{1}H NMR spectroscopy was designed to determine if a relationship existed between the degree of electron donation of aromatic substituents and the rate of reduction of the βeta ketone. A positive correlation would indicate that enhanced nucleophilicity of the amide cabonyl accelerates the attack of the FLP to generate the immediate silyloxonium localized to the amide prior to its stabilizing relaxation into the chelating intermediate. The study was conducted on four β-esteracetanilides with spectral data indicating that the regioselectivity of the system was reverted back to the amide. Yet again, the tris(pentafluorophenyl)borane triethyl silane catalytic system has demonstrated highly tunable selectivity dependent not only on the relative placement of functional groups, but also on their electronic characteristics.

INTRODUCTION

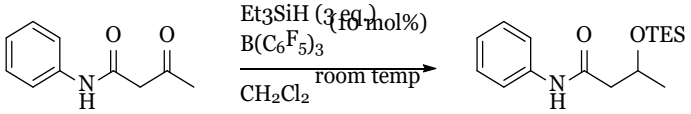
The tris(pentafluoro)phenyl borane-tetrasubstituted silane Frustrated Lewis Pair (FLP) has demonstrated remarkable regio-[1, 2, 3] and stereoselectivity[4, 5, 6, 7, 8] applicable to an extensive range of functional groups including alkenes[9, 7], alkynes[10], alcohols[11, 12, 13, 1], ethers[9, 13], carbonyls[11, 14, 15], and carboxylic acid derivatives[16, 17]. The FLP is an attractive option for synthetic chemists as its reactivity can be controlled depending on the degree of steric hindrance imposed on the silyl center, with less encumbered silanes such as diethyl silane favoring exhaustive deoxygenation of carbonyls, while triethyl silane yields a stable silyl-ether intermediate[18, 3, 19]. A parallel relationship is observed in the steric hindrance of the substrate[13, 16]. Increasing the molar equivalents of silane relative to the substrate also drives the reduction to completion[13, 20]. The catalyst's allure is enhanced by its success in both reactions that generate water as a byproduct or aqueous solvents [21, 22], in contrast to reductants of comparable strength such as lithium aluminum hydride which are explosively incompatible in such environments. The catalyst's efficiency, manipulatable selectivity, and mild reductive potential has elevated the FLP to an exciting sphere of research bridging organic and inorganic chemistry to further understand its synthetic capacity.

Reduction of the highly stable amide bond has previously required the reductive prowess of lithium aluminum hydride. However, this workup endangers the structural integrity of the substrate as it concurrently reduces more electrophilic functional groups such as ketones and aldehydes, necessitating a protecting group for carbonyls such as an acetal while the amide is targeted. On the opposite side of the spectrum, sodium borohydride is relatively weak, limited to the reduction of aldehydes and ketones. The reduction of the amide moiety of acetanilides is of crucial interest to the synthetic community as this backbone is the precursor to a variety of biologically relevant molecules such as potent antibacterial compounds against *Staphylococcus aureus*[23], inhibitors of histone deacetylases to prevent tumor proliferation[24], HIV-1 integrase inhibitors[25], and κappa opioid receptor agonists which relieve pain while minimizing drug dependency by targeting the peripheral nervous system[26]. Curiously, the

introduction of tris(pentafluorophenyl)borane with triethyl silane to acetanilides bearing ether and carbonyl functional groups at the para position resulted in the exclusive and complete reduction of the amide bond to an amine, leaving the more susceptible groups unscathed[3] (Scheme 1). This suggests the FLP complements the expected reactivity of sodium borohydride in the given conditions. Conversely, placement of the carbonyl group βeta to the amide bond reversed the regioselectivity of the reaction so that the ketone was reduced to yield a silyl ether intermediate[3] (Scheme 2).

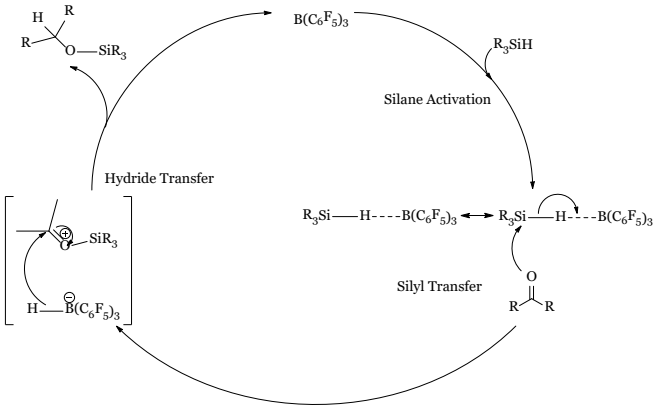


Scheme 1. Selective amide reduction of para-substituted acetanilides; X= methoxy, trifluoromethyl, acetyl, ethyloxy.



Scheme 2. Reduction of β-ketoacetanilides selectively reduces the carbonyl.

These results are in accordance with Piers' proposed reduction mechanism in which the substrate attacks the silyl partner of the FLP to generate a silyloxonium intermediate and hydroborate in-situ[27] (Scheme 3). The superior nucleophilicity of the amide carbonyl ensures that this step is localized to the amide moiety, resulting in its exclusive reduction when the carbonyl groups are segregated to the opposing side of the aromatic ring. However, we propose that a ketone βeta to the silyloxonium generated at the amide will donate stabilizing electron density to the silyl center, forming a six-membered chelating intermediate which activates the more electrophilic carbonyl for reduction (Figure 1).



Scheme 3. Pier's mechanism of reduction in which the step labeled "Silyl Transfer" illustrates the substrate's attack of the FLP.

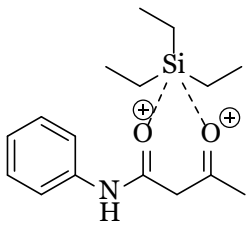
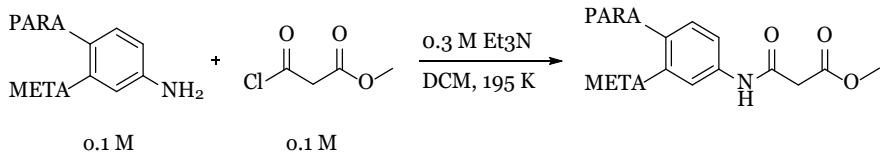


Figure 1. Proposed chelating intermediate bridging the β-keto and amide functional groups.

The purpose of this study is to garner further support for the role of chelation in the regioselectivity of β-ketoacetanilides through a ^{1}H-NMR mediated kinetic study. The rate of the reduction of β-ketoacetanilides, differentially substituted at the meta and para positions, will be compared. The postulated chelating mechanism will be supported if increasingly electron donating aromatic substituents increase the rate of reduction by amplifying the nucleophilicity of the amide through resonance.

METHODS

Chemicals were obtained from Sigma Aldrich and were used without additional purification. Seven β-ester acetanilides were synthesized via a nucleophilic acyl substitution between the substituted aniline and methyl malonyl chloride (Scheme 4). The aniline (5 mmol) and sacrificial base triethylamine (15 mmol) were dissolved in 50 mL of dichloromethane in a 100-mL round bottom flask and chilled by placing the vessel in an insulated acetone/dry-ice bath. The vessel was sealed and purged through the application of Nitrogen gas. Methyl malonyl chloride (5 mmol) was added dropwise over a span of ten minutes. Each reaction was left to stir for at least 24 hours. The reaction was concentrated via rotary evaporation. The β-esteracetanilide was purified via flash column chromatography over silica gel, utilizing a gradient elution progressing from 15% ethyl acetate in hexanes to 50% ethyl acetate in hexanes and washing the column with methanol. The product was identified with TLC chromatography using 40% ethyl acetate in hexanes as the eluent. See Appendix for chemical shift and R_f values.



Scheme 4. Nucleophilic-Acyl substitution of methyl malonyl chloride with differentially substituted anilines at the para or meta position.

Only four β-esteracetanilides- unsubstituted, meta-chloro, meta-nitro, para-ethyloxy- were considered fit to continue testing as the remainder were insoluble in the deuterated chloroform. An appropriate mass of each β-esteracetanilide was weighed to achieve a final concentration of 0.1 M and dissolved in deuterated chloroform (0.6 mL) in a 20-mL scintillation flask. Tris(pentafluorophenyl)borane was subsequently dissolved to achieve a final concentration of 0.01 M (3.1 mg). Immediately prior to introducing the reaction tube to the NMR for analysis, 28.7 µl of triethyl silane (0.3 M) was added via micropipette and the contents of the scintillation flask swirled rapidly for approximately 20 seconds, followed by transferring the contents with a glass Pasteur pipette to the NMR tube. The NMR tubes had been cleaned for thirty minutes in a concentrated HCl bath, rinsing twice with water, followed by acetone.

The experiment was conducted with a Bruker Advance III 400 MHz nuclear magnetic resonance (NMR) spectrometer with Topspin 3.1 software (Bruker BioSpin Corporation, Billerica, MA, USA). The NMR was programmed to leave the tube within the magnet during the entire experiment, with scans obtained every thirty-minutes for 14 hours to track reaction progress. The temperature was set to 295 K, although minute deviations of ± 0.2 K were observed. A deuterated methanol chemical shift thermometer was used immediately prior and following experimentation to accurately determine the temperature. In addition, the temperature was monitored throughout the experiment utilizing the NMR Topspin Bruker program. The parameters were set to a spectral width of 40.5716 ppm centered at -9 ppm. A recycle delay time of 50 seconds was used to ensure complete relaxation of all hydrogen families to enable quantitative integration.

RESULTS AND DISCUSSION

All the products demonstrated a significant upfield shift of the aromatic region. The transfer of the hydrogen to either group would be expected to produce two new splitting patterns in the aliphatic region- a multiplet assigned to the reducing hydrogen and a doublet of doublets assigned to the methylene linker- due to diastereotopic splitting. However, a distinct triplet surfaced in the spectrum of the unsubstituted β-esteracetanilide post-reduction at approximately 2.6 ppm with an array of peaks with an immediately indistinguishable pattern at approximately 3.3-3.6 ppm. See Appendix for chemical shift values.

The product peaks residing in the aliphatic region resembles either the AMX or ABX splitting pattern indicative of three coupled hydrogens- X representing the donated hydrogen to the carbonyl and the A/M or A/B pair representing the hydrogens on the methylene linker. The X hydrogen appears as an apparent triplet despite distinct coupling from both vicinal hydrogens with a chemical shift values ranging from 1.14 to 2.66 ppm. The unsubstituted and meta-nitro products exhibit ABX splitting patterns. Their downfield (3.39-3.53 ppm) array of seven visible peaks integrating at a value approximately two times the X peak, suggesting this mess of peaks is a disordered array of four doublets expected for an AB pattern. Integration reveals the meta-chloro and para-ethyloxy follow the closely related AMX pattern as they each possess three apparent triplets, each integrating for one hydrogen. While three doublet of doublets are normally observed in the AMX pattern, an indistinguishable disparity in the coupling constants of the A and M hydrogen would merge the doublet of doublets to appear as triplets.

These results suggest that the reduction unexpectedly occurred at the amide. Reduction at the ester which lies at the periphery of the molecule would not have dramatically disturbed the aromatic region as observed. Further, ^{1}H NMR literature values predict a chemical shift of 6.51 for the aromatic ortho position, 7.01 for the aromatic meta position, and 6.61 for the aromatic para position of an aniline[28]. These values agree with those observed and indicate partial reduction to the silyl ether proceeded at the amide. Reduction at the amide carbonyl would increase electron density at this carbon and deter the donation of electron density from the nitrogen, shifting the electron donating character of the nitrogen with respect to the ring to more closely resemble the highly stabilizing amino group. Exhaustive reduction, as observed in Scheme 1 of solitary amides, likely did not occur as this product would exhibit a relatively simple spectra of two triplets integrating at two hydrogens each produced by the linking methylene groups and a singlet integrating at three hydrogens produced by the methyl substituent of the ester. In contrast, the integration of the upfield triplet is one hydrogen, and can likely be assigned to the donated reducing hydrogen, split into a symmetrical doublet of doublets by the bridging methylene.

The reversion of regioselectivity to reduce the amide bond within a β-keto system may be due to the stabilizing effect of the oxygen appended to the carbonyl. While chelation activated the highly electrophilic β-ketone for reduction, the presence of lone pairs on the oxygen stabilizes this carbon comparably to the nitrogen of the amide. These results do not negate the postulated chelating mechanism but suggest chelation of the β-carbonyl is not sufficient to realize reduction but requires the carbonyl to be significantly more electrophilic than the amide. Under this proposed model, β aldehydes and ketones would be expected to be exclusively reduced whereas β esters and amides redirect reduction to the acetanilide. This observation further emphasizes the high sensitivity of the catalytic system to substrate characteristics and adds another layer of control for synthetic chemists.

AUTHOR INFORMATION

Corresponding Author

* hackel.taylor@uwlax.edu; tn.hackel@outlook.com

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APPENDIX

^{1}H NMR Data (400MHz, CDCl3); Chemical Shift and R_f Values of β-Ester Acetanilides

Unsubstituted: δ 9.16 (s, 1H, broad), 7.56 (d, J= 7.6 Hz, 2H), 7.34 (t, J= 7.6 Hz, 2H), 7.13 (t, J= 7.4 Hz, 1H), 3.81 (s, 3H), 3.50 (s, 2H); R_f 0.30

Meta-Hydroxy: δ 9.23 (s, 1H, broad), 7.45 (s, 1H), 7.19 (t, J= 8.1 Hz, 1H), 6.89 (d, J= 7.6 Hz, 1H), 6.63 (d, J= 8.2 Hz, 1H), 3.81 (s, 3H), 3.49 (s, 2H); R_f 0.09

Meta-Methoxy: δ 9.15 (s, 1H, broad), 7.30 (s, 1H), 7.23 (t, J= 8.14 Hz, 1H), 7.04 (d, J= 7.9 Hz, 1H), 6.69 (d, J= 8.3 Hz, 1H), 3.81 (s, 3H), 3.49 (s, 2H); R_f 0.24

Meta-Choro: δ 9.30 (s, 1H, broad), 7.69 (s, 1H), 7.40 (d, J= 8.16 Hz, 1H), 7.25 (t, J= 8.1 Hz, 1H), 7.11 (d, J= 7.1 Hz, 1H), 3.82 (s, 3H), 3.49 (s, 2H); R_f 0.32

Para-Ethyloxy: δ 9.46 (s, 1H, broad), 8.03 (d, J= 8.7 Hz, 2H), 7.65 (d, J= 8.7 Hz, 2H), 4.36 (q, J= 7.1 Hz, 2H), 3.83 (s, 3H), 3.52 (s, 2H), 1.39 (t, J= 7.1 Hz, 3H); R_f 0.23

Para-Carboxy: Impure; R_f 0.11-0.26 (smear)

Meta-Nitro: δ 9.64 (s, 1H, broad), 8.45 (s, 1H), 7.99 (d, J= 8.1 Hz, 1H), 7.96 (d, J= 8.3 Hz, 1H), 7.51 (t, J= 8.2 Hz, 1H), 3.84 (s, 3H), 3.54 (s, 2H); R_f 0.21

Para-Nitro: δ 9.77 (s, 1H, broad), 8.23 (d, J= 9.1 Hz, 2H), 7.76 (d, J= 9.1 Hz, 2H), 3.84 (s, 3H), 3.54 (s, 2H); R_f 0.19

^{1}H NMR Chemical Shift Values of Product Aromatic and Aliphatic Region

Unsubstituted: δ 7.13 (t, J= 7.3 Hz, 2H), 6.73 (t, J= 7.3 Hz, 1H), 6.45 (d, J= 7.8 Hz, 2H), AB: Mess of 7 detectable peaks 3.39-3.48 (3H), X: apparent triplet, 2.43 (1H)

Meta-Chloro: δ 7.05 (t, J= 8 Hz, 1H), 6.64 (d, 8 Hz, 1 H), 6.57 (s, 1 H), 6.46 (d, J= 8.1 Hz, 1 H), A: 3.43, (app t, 1 H), M: 3.21 (o, 1 H), X: 1.90 (app q, 1 H)

Meta-Nitro: δ 7.54 (d, J= .8 Hz, 1 H), 7.40 (s, 1H), 7.27 (t, J= Hz, 1H), 6.89 (d, J= .9 Hz, 1H), AB: Mess of 7 detectable peaks 3.43-3.53 (2H), X: 2.66 (app t, 1H)

Para-Ethyloxy: δ 7.87 (d, J= 8.8 Hz, 2H), 6.56 (d, J= 8.8 Hz), A: 3.51 (app t, 1H), M: 3.29 (app t, 1H), X: 1.14 (app t, 1H)

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