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Curtin−Hammett and Steric Effects in HOBt Acylation Regiochemistry

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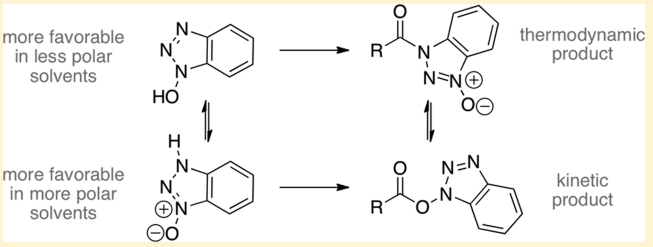
Supporting Information

ABSTRACT: While hydroxybenzotriazole is commonly used in a variety of bond-forming reactions, its acylation has been shown to produce a regiochemical (O vs N) mixture with complex kinetic behavior. Increased steric bulk on the electrophile favors formation of the oxygen-acylated product. Upon standing as a solid, the mixture can isomerize completely to the nitrogen adduct. An equilibrium ratio of regioisomers can be reestablished in solution by adding either nucleophilic or electrophilic reagents, suggesting that the composition of the mixture is not significant to subsequent reactivity. Solvents can affect this regiochemical equilibrium through a Curtin−Hammett effect, where the shift in the tautomeric equilibrium of HOBt in polar solvents biases the reaction toward the oxygen adduct.



INTRODUCTION

A wide variety of coupling conditions have been developed that promote the chemical synthesis of carboxylic derivatives.[1] One method to minimize side reactions is to include a nucleophilic additive that forms an activated ester derivative and subsequently reacts with the desired nucleophile. Some of these additives include *N*-hydroxysuccinimide (HOSu),[2] *N*-hydroxybenzotriazole (HOBt),[3] and ethyl 2-cyano-2-(hydroxyimino)-acetate (OXYMA).[4] All of these additives can be added in the course of a one-pot coupling reaction or the activated ester derivative can be isolated. An effort to maximize synthetic yields led us to isolate HOBt esters of various amino acid derivatives (Figure 1). In several cases, instead of obtaining one clean HOBt adduct, two regioisomers (**3** and **4**) were formed. Similar isomeric results have been reported previously but are poorly understood.[5]

HOBt **1** is unique among these coupling additives in that it can form more than one acylated derivative. HOBt has been isolated in two tautomeric forms[6] and has been shown to be an ambident nucleophile where both the oxygen and an aromatic nitrogen are capable of forming bonds with electrophiles. This regiochemical ambiguity has been seen in the structures of coupling reagents that contain HOBt, such as HBTU,[7] as well as a variety of reactions that form isomeric HOBt adducts.[5] It remains unclear what factors control this regiochemical selectivity, whether conditions can be modified to promote one isomer or the other and how the shifting identity of the activated esters (**3** and **4**) affects subsequent reactivity.

RESULTS AND DISCUSSION

The formation of a variety of acylated HOBt derivatives was undertaken to assess the regiochemical ambiguity (Figure 1). The resulting product ratios for a variety of amino acids (**2a**−**d**) under coupling conditions with HOBt and the coupling reagent ethyldimethylaminopropylcarbodiimide (EDC) are shown in Table 1. Remarkably nonuniform behavior was observed. Less sterically hindered derivatives (such as Boc-glycine **2a**) showed a product ratio that favored the *N*-acyl product **4**, but as the steric bulk increased the product ratio shifted toward the *O*-acyl derivative. This change was subtle for the methyl side chain of alanine (**2b**), more pronounced in the isopropyl side chain of valine (**2c**), and nearly complete in the case of the two methyl groups of Aib (**2d**). In each case where two products were observed, there was doubling of both the HOBt aromatic protons as well as the aliphatic signals. A proportional steric dependence of product ratios was observed for simple carboxylic acids as well (**2e**−**i**). The accumulated data suggests that the *N*-acyl isomer **4** has greater steric limitations on its formation, and acylation with bulkier substrates favors the formation of the *O*-acyl derivative **3** that contains an extra atom between the HOBt rings and the acylating agent. The steric effect is consistent within a group of similar molecules, but comparison of amino acids and simple carboxylic acids suggests that this is not the only effect. These regiochemical results are consistent with the scattered reports of HOBt acylation existing in the literature, where both mixtures and pure compounds have been reported. For example, when Aib was chosen to probe the maximal steric deterrent for coupling only the *O*-acyl form was observed,[8] but less sterically demanding substrates led to mixtures.[5] One additional point of note is that only one regioisomer was ever observed with acylated HOAt derivatives under any reaction conditions and no isomerization was observed, suggesting that these effects are not general to all similar derivatives.[9]

One aspect of these reactions that has not been reported previously is the isomerization of **3** to **4** upon formation of a solid.

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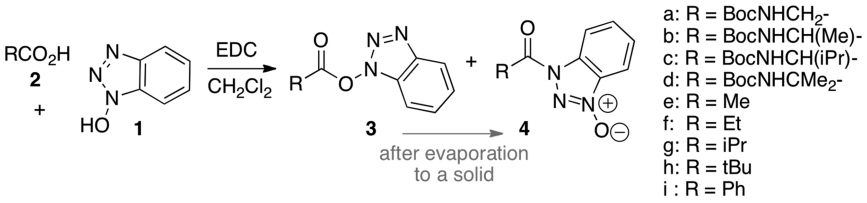

Figure 1. Creation of acylated HOBt regiochemical isomers.

Table 1. Isolated Product Ratios for Reaction of Carboxylic Acid Derivatives (2a−i) with HOBt and EDC

acylating agent	*O*-acyl **3**/*N*-acyl **4**
Boc-Gly-OH **2a**	25:75
Boc-Ala-OH **2b**	42:58
Boc-Val-OH **2c**	70:30
Boc-Aib-OH **2d**	97: 3
$MeCO_2H$ **2e**	43:57
$EtCO_2H$ **2f**	48:52
$iPrCO_2H$ **2g**	75:25
$tBuCO_2H$ **2h**	99:1
$PhCO_2H$ **2i**	99:1

In the preliminary stage of the syntheses found in Table 1, it was noticed that the product ratios were often dependent on the time frame of the reaction and workup. Some purification conditions and NMR acquisition led to the product ratios reported in the table, while delays led to an increase in product **4**. Indeed, when samples that contained a mixture of **3** and **4** were allowed to stand as a solid for a period of time, exclusively *N*-acyl product **4** was often observed, without any signs of degradation products. As a result, all of the data in Table 1 reflect immediate workup and characterization. This isomerization will be addressed further in the kinetics results below.

Kinetics. A more detailed kinetic analysis of HOBt acylation was undertaken and proved to be quite enlightening in regard to the regiochemical selectivity. The acylation of HOBt with propionyl chloride was chosen as a characteristic reaction, and the kinetic progress was monitored in various NMR solvents. Figure 2 shows the percentages of the *O*-acyl isomer **3f** in the mixture of **3f** and **4f** in four solvents. In each case, the acyl chloride is consumed before NMR acquisition is possible (within 3 min), and the *O*-acyl product is formed exclusively at early time points. As each experiment progressed, an isomerization was observed that led to the final equilibrium product ratios shown in Table 2. While the reaction trends are the same in every solvent, the final equilibrium product ratio was different in each solvent. The reaction of propionyl chloride in $CDCl_3$ showed a final product ratio that was nearly identical to propionic acid under coupling conditions, slightly favoring the N-acylation product **4f**. Moreover, this product ratio was unchanged by performing the reaction at reflux, suggesting that an equilibrium mixture had been achieved. When benzene, acetonitrile, or acetone was used as the solvent the reaction favored O-acylation product **3f**, each to a different degree.[10] Identical product ratios are observed when triethylamine is used as a base, but the equilibrium is reached at a much faster rate.[11]

This equilibrium behavior appears to be an example of the Curtin−Hammett principle,[12] where the results in various solvents

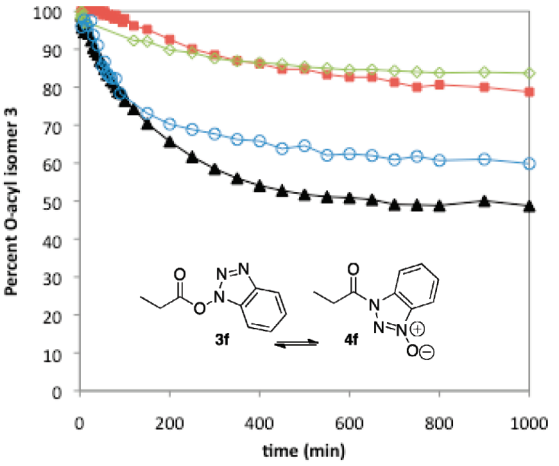

Figure 2. Kinetics for the reaction of propionyl chloride and HOBt in various solvents. ▲ = $CDCl_3$; ○ = C_6D_6; ■ = CD_3CN; ◇ = $CD_3C(O)CD_3$.

Table 2. Final Product Ratios for the HOBt Acylation with Propionyl Chloride in NMR Solvents

reaction solvent	*O*-acyl **3f**:*N*-acyl **4f**
$CDCl_3$	47:53
$CDCl_3$ at reflux	47:53
C_6D_6	58:42
CD_3CN	78:22
$CD_3C(O)CD_3$	84:16

reflect a balance of tautomeric equilibrium, relative nucleophilicity, and product stability. HOBt has been shown to exist in two tautomeric forms (**1** and **1′** Figure 3) with more polar solvents biasing this equilibrium toward the zwitterionic form.[6] The initial formation of the *O*-acyl derivative **3** in all solvents suggests that the reaction at the oxygen atom proceeds through a lower activation energy than the ring nitrogen, presumably due to a more accessible steric approach. The ultimate formation of *N*-acyl product **4** upon formation of a solid suggests this is the thermodynamic product.[13] The greater stability of the nitrogen/carbonyl bond over an oxygen/carbonyl bond appears to be similar to the relative stability of other amide and ester derivatives. Presumably over time, molecules in equilibrium can overcome the higher barrier to form N-acyl adduct **4**. There appear to be two competing solvent effects. The shift toward the *O*-acyl product **3** in benzene in comparison with chloroform is consistent with a disfavoring of the zwitterionic *N*-acyl product **4** in the more nonpolar conditions. An alternative effect is seen with acetone and acetonitrile as solvent, where presumably the more

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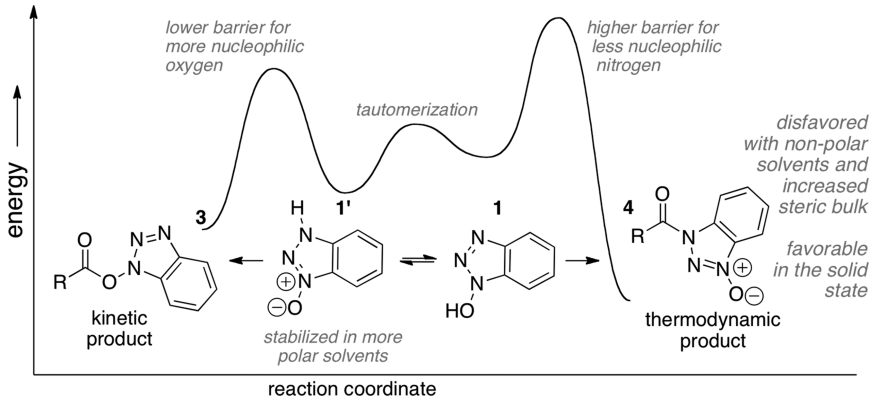

Figure 3. Curtin–Hammett equilibrium of HOBt tautomers and acylated HOBt adducts.

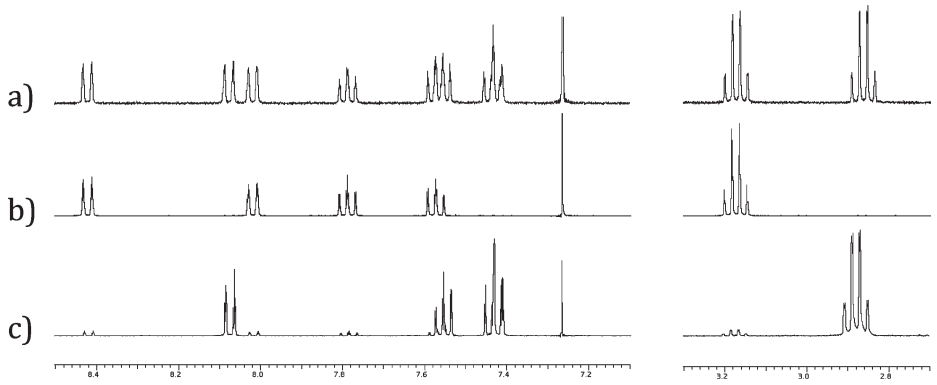

Figure 4. Regiochemical mixture and enriched isomers from the reaction of propionyl chloride and HOBt: (a) reaction mixture in $CDCl_3$; (b) *N*-acyl form **4f** after several days as a solid; (c) enriched *O*-acyl form **3f** (95% purity) isolated from immediate workup.

polar product should be favored. The observed preference for O-acylation correlates with the change in relative tautomerization of the HOBt nucleophile in solution during the course of the reaction, with more polar solvents stabilizing the zwitterionic tautomer **1**′ and shifting the equilibrium toward the *O*-acyl isomer **3**.[14] This is the example of the Curtin–Hammett principle where the balance of tautomers or transition states exhibits a greater influence on the reaction than does product stability.

These syntheses and kinetic profiles illustrated methods to form each regioisomer in relative purity (Figure 4). The *O*-acyl derivative **3** could be isolated from short reaction timeframes without added base, followed by immediate extraction with water.[15] In this manner, the *O*-acyl isomer could be obtained in 95% purity. The *N*-acyl derivative **4** could be obtained merely by letting the compound stand in the solid state for a matter of days, and complete isomerization was observed for simple carboxylic acids. Conversely, when a mixture of **3** and **4** was retained in $CDCl_3$ solution, the product ratio was unchanged over a period of three weeks.[10] This was found to be the case independent of the starting ratio itself. These results suggest that once the purified product ratio is established it is maintained in solution, but the formation of the more stable *N*-acyl **4** product is favored in the solid.

While any existing ratio of **3f** and **4f** was unchanged in pure solvent, additional nucleophilic or electrophilic reagents led to an isomerization back to the equilibrium ratio reported in Figure 2 (see Figure 5, ▲). When the pure *N*-acyl derivative **4f** was

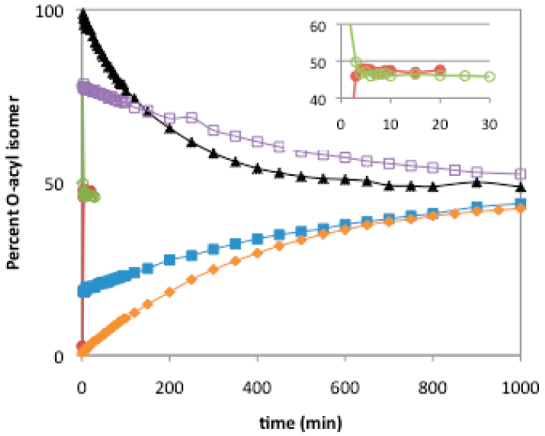

Figure 5. Re-equilibration of mixtures of **3f** and **4f** to the same 47:53 ratio. The percentage of *O*-acyl **3f** in the **3f**/**4f** mixture are shown. All reactions are in $CDCl_3$. ▲ = propionyl chloride + HOBt (2 equiv); ● = *N*-acyl derivative **4f** + DMAP; ○ = enriched *O*-acyl derivative **3f** + DMAP; ◆ = *N*-acyl derivative **4f** + HOBt; ■ = enriched *N*-acyl derivative **4f** + EtCOCl; □ = enriched *O*-acyl derivative **3f** + EtCOCl.

dissolved in $CDCl_3$ in the presence of DMAP, the 47:53 equilibrium ratio was almost immediately reestablished (Figure 5, ●). Similar behavior was observed when DMAP was added to a mixture enriched in the *O*-acyl derivative **3f** as well (Figure 5, ○). This would suggest that the DMAP functions as a nucleophilic

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catalyst as shown in Figure 6a to form **5**, liberating HOBt which can subsequently react to re-establish an equilibrium of **3f** and **4f**. Addition of HOBt itself also led to the re-equilibration to the 47:53 ratio at a much slower rate (Figure 5, ♦). A similar slower re-equilibration was observed when additional acyl chloride was added to $CDCl_3$ solutions enriched in either regioisomer (Figure 5 ■, □). All kinetic curves converge on the equilibrium ratio of 47:53 given enough time.[10] It is more difficult to suggest exactly how the acyl chloride accelerates the rate over solvent alone, but the excess of acyl halide would preclude the liberation of HOBt. One possibility is shown in Figure 6b, where the acylation of the HOBt oxygen atom of the *N*-acyl adduct **4**, followed by breakdown of the bis-acylated HOBt adduct **6**.[16] When similar experiments with added nucleophile were performed in other solvents, the re-equilibration reached values similar to the data in Table 2.[10]

Reactivity toward Nucleophilic Attack. Previous results have suggested that the *O*-acyl derivative **3** can be more reactive

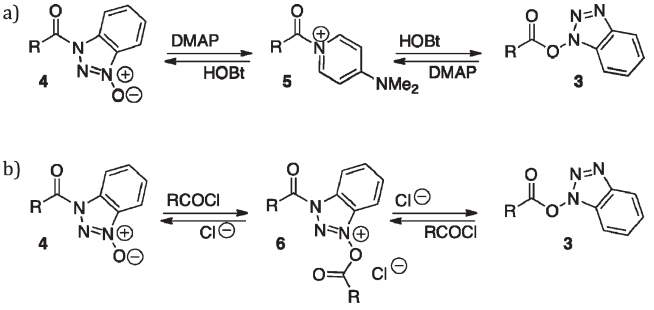

Figure 6. Potential mechanisms for the re-equilibration of *N*-acyl HOBt through (a) nucleophilic catalysis or (b) electrophilic catalysis.

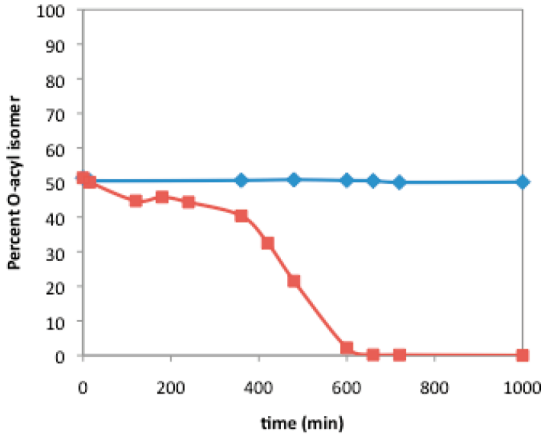

Figure 7. Kinetic profile for two sample containing both **3f** and **4f**. ◆ = solution in $CDCl_3$; ■ = evaporated to a solid.

to nucleophilic attack than the *N*-acyl isomer **4**.[5] In our hands, when a mixture of **3f** and **4f** was reacted with butylamine, both isomers were consumed equally. This is complicated, however, by the re-equilibrations described above. When a solution of pure *N*-acyl isomer **4f** was reacted with a substoichiometric amount of amine, the *O*-acyl isomer **3f** was formed as well as the product amide. Presumably, the nucleophilic attack liberated HOBt which subsequently re-established the equilibrium ratio of **3** and **4**. This competing process makes it impossible to determine if both isomers are indeed reacting equally, or if one isomer reacts followed by re-establishment of the equilibrium ratio. One exception was the reaction of an equilibrium mixture of **3f** and **4f** in $CDCl_3$ at 0 °C with substoichiometric *tert*-butylamine. In this case, some *N*-acyl isomer **4f** remained in solution and the *O*-acyl isomer **3f** was completely consumed, while HOBt precipitated from solution. It is thought that the more electrophilic *O*-acyl derivative reacted preferentially and precipitation of HOBt from the reaction at low temperature precluded re-equilibration. In general, the *O*-acyl isomer does appear to be more electrophilic, but liberation of HOBt can result in the subsequent formation of an equilibrium mixture of both regioisomers. This would mean that in many cases the composition of the acylated mixture would have little effect on subsequent reactivity.

Formation of *N*-Acyl Isomer in Solid. The ultimate isomerization to the *N*-acyl isomer **4** upon isolation of the pure solid is more challenging to address mechanistically. Figure 7 shows parallel reactions that follow the progress of a sample containing both **3f** and **4f**, one portion being kept in $CDCl_3$ solution while the other portion was evaporated to a solid. The solution again remained unchanged, while the solid ultimately isomerized to the *N*-acyl form **4f** through a complex kinetic profile, without the formation of other products. The results in Figures 2 and 5 suggest that if any reaction occurs in solution it will lead to the establishment of an equilibrium of both acylated-HOBt regioisomers, with nucleophilic catalysis occurring fairly quickly and electrophilic catalysis occurring more slowly. Neither of these processes occurs at any appreciable rate in solution in the absence of catalyst, with an existing product ratio being stable for a matter of weeks. The ultimate establishment of the thermodynamic product in the solid requires both the cleavage of existing bonds, and reformation of the other isomer without degradation. One could imagine this resulting through either a greater shift toward nitrogen nucleophilicity in the absence of solvent, or through a process that is not observed in solution. There is no NMR evidence of hydrolysis to liberate HOBt to subsequently function as a nitrogen nucleophile and no solvent polarity where reaction at nitrogen is exclusive (Table 2). One possibility is that a bimolecular mechanism would become more favorable at higher concentrations, such as in a solid. The proposed mechanism in Figure 8 shows a bimolecular electrophilic process with the more electrophilic *O*-acyl substrate reacting with another molecule of

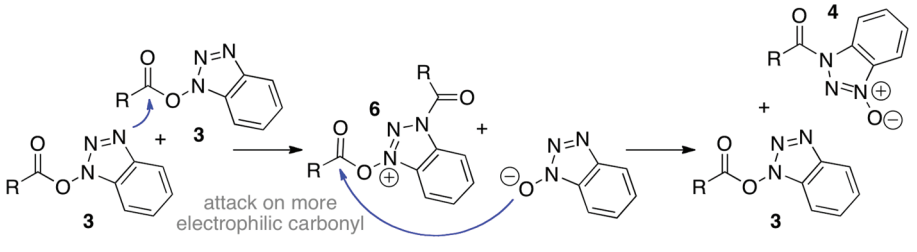

Figure 8. Possible mechanism for the isomerization to **4** observed in the solid state.

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itself to form the bis-acylated adduct **6**. The liberated OBt anion could then perform a nucleophilic attack on the more electrophilic *O*-acyl carbonyl of **6**. As the more electrophilic of the two species, the *O*-acyl derivative **3** should react preferentially through this bimolecular process at a faster rate than the corresponding attack on the *N*-acyl **4**.[17] This process would ultimately transform two molecules of **3** into one molecule each of **3** and **4**. While it would be challenging to predict such a rearrangement, the end result would be the formation of a more thermodynamically stable molecule **4**. If the more electrophilic *O*-acyl adduct **3** were to continue to react in preference over the more stable *N*-acyl adduct **4**, in time all of the *O*-acyl derivative **3** would be consumed.

CONCLUSIONS

HOBt displays a variety of intriguing acylation behaviors, exhibiting regiochemical changes throughout the kinetic course of reactions. Its acylation chemistry is variable, dependent on local steric and tautomeric evironment. This is further modified by the existence of equilibrium in solution and isomerization to the thermodynamic product as a solid. These competing processes make quantitative rate determinations difficult. Subsequent reactivity toward nucleophiles is biased toward the *O*-acyl form, but catalyzed isomerization means that the starting ratio of regioisomers is of limited importance.

EXPERIMENTAL SECTION

Synthesis of Acylated HOBt Mixtures. General Procedure for the Coupling of Carboxylic Acids to HOBt. Carboxylic acids were dissolved in 50 mL of dichloromethane. To this were added hydroxybenztriazole (1.1 equiv) and EDC (1.2 equiv), and the reaction was stirred for 16 h. The organic solution was washed with 10% HCl and saturated $NaHCO_3$. After treatment with Na_2SO_4, the solution was evaporated to dryness under vacuum. A white solid was formed in each case. NMR product ratios were reported from crude mixtures following extraction and minimal vacuum.

Kinetic Analysis of HOBt Acylation. All kinetic experiments were performed at a final HOBt concentration of 10 mM. For a typical acylation procedure, HOBt (1.2 mg, 7.8 μmol) was dissolved in $CDCl_3$ (705 μL) to a final concentration of 11.11 mM. The HOBt solution (450 μL) was transferred to an NMR tube, and a data point was acquired for t = 0 min. A second solution was prepared by dissolving propionyl chloride (5.0 mg, 54 μmol) in $CDCl_3$ (1080 μL) to a final concentration of 50 mM. The acyl chloride (50 μL) was added to the NMR tube so that the final concentration was 5 mM. Data points were acquired as quickly as permitted for the first 10 min, followed by subsequent regular intervals through 1000 min. Ratios described graphically reflect the percent composition of *O*-acyl **3f** and *N*-acyl **4f** derivatives within the sum of the two. Signals corresponding to the *O*-acyl **3** and *N*-acyl **4** derivatives were determined by comparison with enriched samples.

Enriched 1*H*-Benzo[*d*][1,2,3]triazol-1-yl Propionate (3f). Propionyl chloride (2.8 mg, 30 μmol) was dissolved in CD_3CN (100 μL). A second solution containing HOBt (10.1 mg, 65.9 μmol) in CD_3CN (500 μL) was added to the acyl chloride, and the solution was allowed to stand for 1 min. The reaction was quenched by pouring the solution into 5 mL of $CDCl_3$ and 10 mL of ice−water. The organic layer was separated and dried with sodium sulfate. The resulting solution contained 95% *O*-acyl isomer **3f** and 5% *N*-acyl isomer **4f** based on NMR integration. Major product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.9 Hz, 1H), 7.57 (t, J = 8.7 Hz, 1H), 7.47 (m, 2H), 2.88 (q, J = 7.4 Hz, 2H), 1.40 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 128.9, 125.0, 120.7, 108.4, 25.1, 8.9.

1-Propionyl-1*H*-benzo[*d*][1,2,3]triazole 3-Oxide (4f). The *N*-acyl regioisomer was formed in a variety of samples upon standing as a solid at room temperature. The kinetics of isomerization was investigated using a sample that contained both regioisomers and was evaporated to a solid under reduced pressure. At various time points the ratio of **3** and **4** was determined via NMR integration, ultimately resulting in pure *N*-acylated product (**4f**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.79 (t, J = 8.4 Hz, 1H), 7.58 (t, J = 8.4 Hz, 1H), 3.17 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 133.2, 132.7, 132.5, 126.9, 116.2, 115.7, 28.8, 8.3; HR-MS (ESI) calcd for [$C_9H_9N_3O_2$] requires m/z 192.0773, obsd 192.0772.

ASSOCIATED CONTENT

Supporting Information. Characterization of product mixtures and kinetic analyses for all substrates and conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

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