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[1,3]-Claisen Rearrangement via Removable Functional Group Mediated Radical Stabilization

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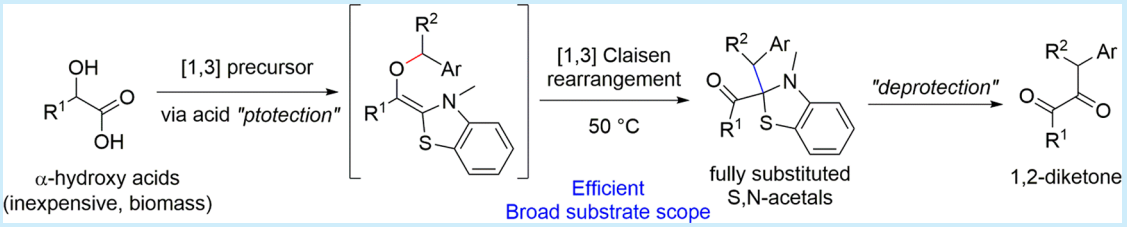

ABSTRACT: A thermal O-to-C [1,3]-rearrangement of α-hydroxy acid derived enol ethers was achieved under mild conditions. The 2-aminothiophenol protection of carboxylic acids facilitates formation of the [1,3] precursor and its thermal rearrangement via stabilization of a radical intermediate. Experimental and theoretical evidence for dissociative radical pair formation, its captodative stability via aminothiophenol, and a unique solvent effect are presented. The aminothiophenol was deprotected from rearrangement products as well as after derivatization to useful synthons.

The thermal [1,3]-rearrangement of O-alkyl enolates was reported by Claisen in 1896,[1] well before the famous [3,3]-Claisen sigmatropic rearrangement of O-allyl enolates in 1912.[2] The [3,3]-rearrangement exhibits many essential aspects of an ideal reaction, namely mild conditions and a waste-free rearrangement for the regio- and stereoselective synthesis of polyfunctionalized products.[3] On the other hand, although the thermal [1,3]-rearrangement is theoretically a similar waste-free process, only a handful of reports have appeared in the literature with very high-temperature requirements, narrow substrate scopes, and often poor yields. A thermally allowed pericyclic pathway is presumably unattainable due to the constrained transition state with inversion at the migrating center. The dissociative radical pair mechanism for the reported methods is generally accepted and often attributed to its inefficiency, substrate dependency, and the dearth of examples (Figure 1a).[4] The substrate dependency with a narrow scope was exemplified by an accidental [1,3] migration of highly substituted classes of ketene silyl ethers discovered by the Shiina group.[4q] The thermal rearrangement proceeds efficiently at 100 °C, but only with a fully substituted C-3 carbon (R^1, $R^2 \neq H$). On the other hand, other dissociative radical pair rearrangements from highly reactive starting materials that proceed under mild conditions such as anionic [1,2]-Wittig and zwitterionic Stevens rearrangements are efficient and synthetically valuable.[5] A general and milder radical [1,3]-Claisen rearrangement could, therefore, represent an efficient and synthetically significant process.

We reasoned that a reactive enol ether and stable corresponding α-keto radical intermediate would reduce the activation energy for thermal [1,3]-rearrangement via homolytic bond cleavage. We envisioned that inexpensive biomass α-hydroxy acids could be converted to derivative **5**, which would facilitate a mild 1,3-rearrangement for two reasons.[6] First, the enol ether conjugated with the three heteroatom lone pairs of electrons is electron-rich and expected to be activated for a homolytic bond cleavage (**5** to **6**).[7] Second, the resulting α-keto radical intermediate (**III**) should achieve enhanced stability via a push−pull captodative effect.[8] The extended conjugations in captodatively stable radicals lead to polarization and should enjoy a unique solvent stabilization for further reduction in bond dissociation energy.[9] Herein, we report a facile and efficient thermal [1,3]-Claisen rearrangement of α-hydroxy acid derivatives. The enhanced reactivity of an intermediary enol ether and the stability of a subsequent radical intermediate was achieved by the protection of the carboxylic acid group with a removable 2-aminothiophenol for its substrate independent reactivity. The reaction mechanism and its efficiency are supported by both experiments and computations.

We started our exploration with the protection of the carboxylic acid with 1,2-phenylenediamine, 2-aminophenol,

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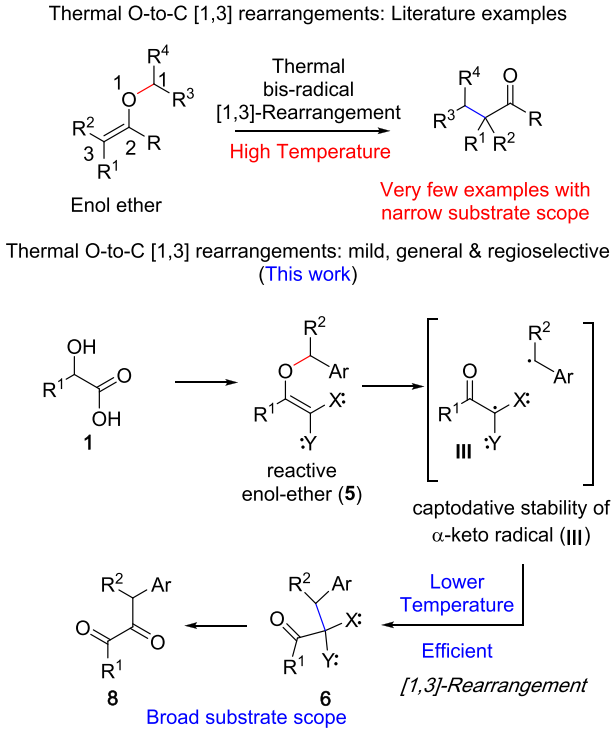
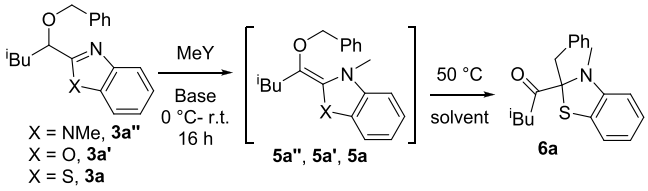


Figure 1. Thermal [1, 3]-Claisen rearrangements

and 2-aminothiophenol, respectively. The protected acid derivatives were O-benzylated (**3**), followed by *N*-methylation with methyl triflate in a minimum amount of DCM for their clean formation of the corresponding salts (**4**; see Supporting Information (SI) for details).[10] The formation of a [1,3] precursor enol ether (**5**) and its proposed rearrangement were studied via an operationally simple treatment of weak base DBU *in situ* at room temperature followed by warming. DMSO was chosen as the solvent to study the rearrangement with an anticipation that a compatible polar solvent would reduce the activation energy further by stabilizing the captodative radical (**III**), leading to a facile or faster product formation.[9] Carboxylic acid derivatives of 1,2-phenylenediamine and 2-aminophenol (**3a″**, **3a′**) led to the smooth formation of *N*-methyl salts (**4a″**, **4a′**; see SI), but failed to rearrange at ambient temperature followed by decomposition at higher temperature (entries 1, 2). With 2-aminothiophenol derivative **3a**, we were delighted to observe the partial formation of [1,3]-rearrangement product **6a** (~22%) at room temperature (Table 1, entry 3). The rate of thermal rearrangement increased substantially at 50 °C for its completion in 8 h to form the [1,3] product in 90% yield (entry 4). With **3a**, we screened other bases and alkylating reagents to find both DBU and K_2CO_3 as efficient bases and methyl triflate as the optimal alkylating agent in DMSO (entries 5−8). As anticipated, the rearrangement in less polar solvents such as toluene was slower and afforded a lower yield (69%, entry 9). Other solvents were screened for their effect on the rearrangement (entries 10−14) which showed DMSO as the best solvent with yields and rate of rearrangement roughly following the solvent polarity.

With the development of a mild and efficient rearrangement condition, we explored the substrate scope to find its generality. Different α-hydroxyacid derivatives with alkyl, benzyl, and aryl groups (R^1) were efficient for the synthesis of various alkyl and aryl ketones (Figure 2, **6a−h**). The

Table 1. Thermal Rearrangement for α-Hydroxy Acid Derivatives[a]



entry	X	MeY	base	solvent	time (h)	yield (%)
1[b]	NMe	MeOTf	DBU	DMSO	24	ND
2[b]	O	MeOTf	DBU	DMSO	24	ND
3[c]	S	MeOTf	DBU	DMSO	24	22
4	S	MeOTf	DBU	DMSO	8	90
5	S	MeOTf	K_2CO_3	DMSO	8	92
6	S	MeOTf	$KHCO_3$	DMSO	16	<5
7	S	Me_2SO_4	K_2CO_3	DMSO	8	40
8[d]	S	MeI	K_2CO_3	DMSO	8	27
9	S	MeOTf	K_2CO_3	PhMe	16	69
10	S	MeOTf	K_2CO_3	PhMe	16	69
11	S	MeOTf	K_2CO_3	DCE	12	77
12	S	MeOTf	K_2CO_3	THF	12	72
13	S	MeOTf	K_2CO_3	DMF	10	79
14	S	MeOTf	K_2CO_3	DMA	10	86

[a]Conditions: All reactions were performed on a 0.2 mmol scale with 1.5 equiv of MeY and 2 equiv of bases in 2 mL of solvent (0.1 M) at 50 °C. [b]rt−100 °C. [c]rt. [d]*N*-Methylation step at 0−40 °C.

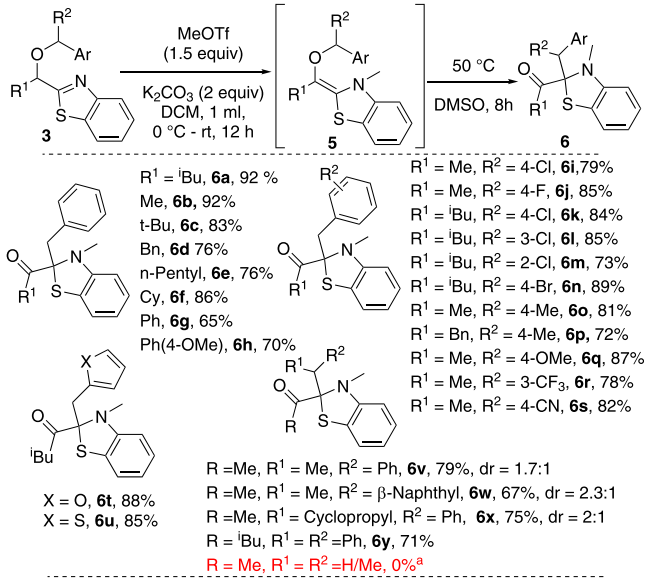


Figure 2. Substrate scope. Reaction conditions: Methyl triflate (0.3 mmol) was added to the substrate (0.2 mmol) and K_2CO_3 (0.4 mmol) in 1 mL of DCM (0.2 M) at 0 °C for 12 h, followed by addition of DMSO (2 mL, 0.1 M) and heating at 50 °C for 8 h. [a]Up to 100 °C after DMSO addition.

generality of migrating groups was tested next with R^1 as alkyl groups. A broad variety of substituents on the phenyl ring of the migrating benzyl were equally effective. For example, fluoro, chloro, and bromo at C-4 with either methyl or isobutyl as R^1 rearranged to form corresponding products (**6i−k**) in good yields. With R^1 = ^{i}Bu, *ortho-*, *meta-*, and *para-*chlorobenzyl substituents were tested to examine electronic and steric effects. Both *para-* and *meta-* resulted in similar high

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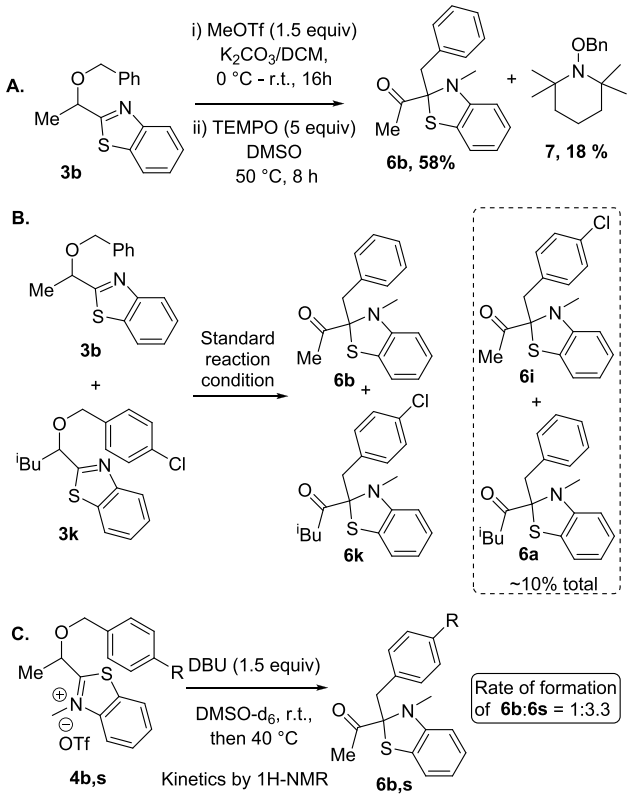
yields (**6k**, **6l**), while *ortho*- led to slightly diminished product formation (**6m**). Electron-donating groups at C-4 such as methyl and methoxy (**6o**−**q**) were found to be effective. Gratifyingly, electron-deficient groups such as trifluoromethyl at C-3 (**6r**) and cyano (**6s**) at C-4 (**6m**) were also well tolerated. C-2 substituted heteroaromatic furan (**6n**) and thiophene (**6o**) also led to the rearranged product under the optimized reaction conditions in good yields. α-Substituted benzyl groups were tested next for their thermal [1,3] migration. The rearrangements with tertiary migrating groups proceeded at a faster rate than the secondary benzyl to furnish products in good overall yields with low to moderate diastereoselectivities. The 1-phenylethyl group migrated with a 79% yield and 1.7:1 diastereomeric ratio, and 1-β-naphthylethyl rearranged to 67% product with 2.3:1 diastereoselectivity. Interestingly, the 1-phenylcyclopropyl ethyl group migrated efficiently (yield 75%, dr = 2:1) without any ring-opening product.[11] The low diastereoselectivities in these products might be a combination of poor d.r. of in situ formed [1,3] precursors and dissociative nature of the rearrangement. A 1,1-bisphenylmethane (**6y**) also migrated efficiently to yield 71% of the rearranged product. Alkyl groups such as methyl, ethyl, and isopropyl as the migrating group remained unreactive under the optimized reaction conditions, and heating at higher temperature led to a complex reaction mixture, presumably via multiple air oxidation paths.[12]

With the establishment of a broad substrate scope for the thermal [1,3]-rearrangement protocol, we next conducted mechanistic studies on this facile migration. First, a radical trap reaction with TEMPO was conducted to obtain direct evidence for a *bis*-radical path. A 1 equiv amount of TEMPO did not alter the product formation significantly, although we detected a TEMPO trapped benzyl radical by HRMS analysis of the crude reaction mixture. Increasing the TEMPO to 5 equiv led to a lowering of yield for the [1,3] product (58%) along with 18% isolated TEMPO trapped product (Scheme 1A). Next, we carried out a crossover experiment with **3a** and **3i** (Scheme 1B), which mainly resulted in intramolecular products **6a** and **6i** along with ∼10% total cross-products **6b** and **6h**. The partial trapping of radicals via TEMPO and a minor amount of crossover product formation indicate a solvent cage recombination of *bis*-radical intermediates. To further distinguish between radical versus ionic paths, we compared the rate of rearrangement for the 4-cyanobenzyl migrating group to the parent benzyl group (Scheme 1C). The 4-cyano substituent is expected to reduce the rate of the ionic reaction[13] while accelerating the radical reaction path.[14] The kinetic experiments via ^{1}H NMR monitoring in DMSO-d_6 at 40 °C resulted in a 3.5 times faster reaction with the 4-cyano substrate, further supporting the radical mechanism (see SI for details).

To compare the relative energy required for thermal radical pair [1,3]-rearrangements, we calculated the ΔG associated with the bond dissociation step for Claisen,[1] Shiina,[4g] and our system using DFT (ωB97XD/6-31+G(d,p)) (Scheme 2).[9,15] We chose the migrating group as benzyl for all three systems to correlate the effect of α-ketyl radical stability (**I**, **II**, and **III**) on the bond dissociation step. The gas-phase ΔG for the homolytic cleavage of the Claisen system is 34.3 kcal/mol, consistent with the very high temperature for its rearrangement. For the fully substituted Shiina system, the ΔG is 12.9 kcal/mol, while for our 2-aminothiophenol protected system the ΔG is 13.0 kcal/mol, in line with their unusually facile

Scheme 1. Mechanistic Experiments



thermal rearrangement (Scheme 2A). The fact that our substrates rearrange effectively at a lower temperature indicates further stabilization via solvent on the captodatively stable radical **III**. To estimate the relative solvent effects, we first determined the ΔG's in solvents with an increasing dielectric constant for these three α-keto radicals. The calculations show a considerably higher magnitude of stabilization (5.0 vs 1.8 vs 1.3 kcal/mol from gas-phase to DMSO) for radical **III** over radical **II** and **I**. The origin of this solvent stabilization was attributed to their polarization which was examined via spin densities for radical **II** and **III** in different solvents (Scheme 2B) using the SMD solvation model.[9,16] The computations show that the reduction in spin density at radical carbon in a higher polarity solvent was greater in magnitude for our system (**III**) compared to the α-ester radical **II**. Conversely, the spin density on electron donor nitrogen in **III** increased significantly, while no significant change was observed on α-carbons of **II**. Both the spin density distribution and ΔG calculation in different solvents shows our captodatively stable radical **III** was more polarizable than a typical α-keto radical and exerted higher stabilization in polar solvents. The solvent effect was tested experimentally, which showed a 1.6-fold rate enhancement in DMSO compared to toluene at 40 °C. We observed significant spin density on sulfur (0.12), which is indicative of its superior effect on radical **III** stabilization and success over other carboxylic acid protecting groups tested.

Finally, we demonstrated the removal of the 2-aminothiophenol from the [1,3] rearranged products. Several reported S,N-acetal deprotection reagents were unsuccessful, but $AgNO_3$ at 60 °C afforded the desired products **8** in 55−64% yield.[17] Optimization with various silver salts led to cleaner deprotection with $AgBF_4$ in MeCN/H_2O (3:1) at 60 °C for 2 h to the diketone products with various C-2

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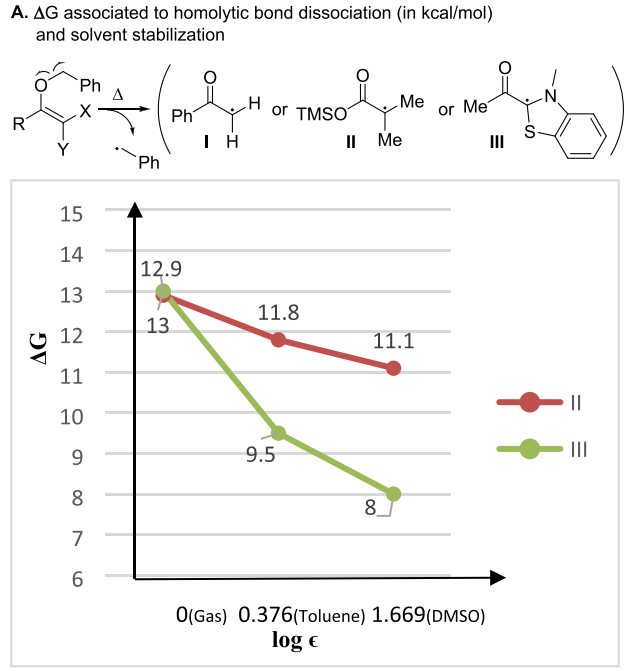
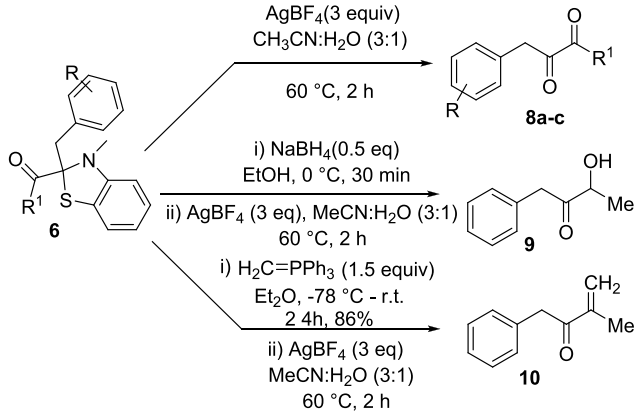
Scheme 2. Captodative Stability and Solvent Effects



substituted rearranged products (**8a−c**) (Scheme 3). We also took advantage of the regioselectively protected diketone products to modify the unprotected ketone to an alcohol and alkene followed by deprotection to obtain selectively one regioisomer of the α-hydroxy alcohol **9** and α,β-unsaturated ketone **10**, respectively.[18]

In conclusion, inexpensive, stable, and naturally abundant α-hydroxy acids were converted to 2-aminothiophenol derived enol ether precursors for their thermal [1,3]-rearrangements under ambient conditions. The aminothiophenol derivative of carboxylic acids led to protection, enol ether formation, and most importantly radical stabilization for mild and general thermal [1,3]-rearrangements. Good to excellent yields were achieved with both alkyl and aryl α-hydroxy acids and a large variety of migrating groups. Mechanistic studies support a dissociative radical pair mechanism and solvent cage recombination. Computational studies support our hypothesis

Scheme 3. Derivatization of [1,3] Products



for facile reaction and provide evidence for further solvent stabilization. The S,N-acetal of the rearrangement products and their derivatives were deprotected efficiently with good yields for the synthesis of 1,2-diketones, as well as an unsymmetrical α-hydroxy ketone and α,β-unsaturated ketone. We are currently exploring the possibility of stereotranslation from chiral substrates via stereoretentive [1,3]-rearrangements.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04109.

Experimental details; characterization of compounds; Computational studies; NMR spectra (PDF)

FAIR data, including the primary NMR FID files, for compounds **S1−2**, **S4−5**, **S7−8**, **S11−15**, all **3** and **6**, **4b**, **4s**, **8a−c**, **9**, **10** (ZIP)

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Notes

The authors declare no competing financial interest.

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