

Catalytic Conjugate Additions of Carbonyl Anions under **Neutral Aqueous Conditions**

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Abstract: The conjugate addition of carbonyl anions catalyzed by thiazolium salts that is fully operative under neutral aqueous conditions has been accomplished. The combination of α-keto carboxylates and thiazolium-derived zwitterions produces reactive carbonyl anions in a buffered protic environment that readily undergo conjugate additions to substituted α,β -unsaturated 2-acyl imidazoles. The scope of the reaction has been examined and found to accommodate various α -keto carboxylates and β -aryl substituted unsaturated 2-acyl imidazoles. The optimal precatalyst for this process is the commercially available thiazolium salt 5, a simple analogue of thiamin diphosphate. In this process, no benzoin products from carbonyl anion dimerization are observed. The corresponding 1,4-dicarbonyl compounds can be efficiently converted into esters and amides by way of activation of the N-methylimidazole ring via alkylation.

Introduction

Chemical processes in nature catalyzed by enzymes are not only essential for the efficient implementation of life processes, but also serve as elegant inspirations for the development of new strategies regarding bond-forming reactions.^{1,2} The biochemical investigations of many fundamental enzymatic processes have influenced recent advances in efficient chemical transformations. A particularly intriguing biological pathway involves the production of acetylCoA from pyruvic acid (1, eq 1). This reaction efficiently converts **1** into a carbonyl anion in the presence of thiamin diphosphate contained within an α -keto acid dehydrogenase active site.³⁻⁷ This elegant transformation is the archetype of an Umpolung process: a polarity reversal manifold that converts a normally electrophilic carbonyl carbon atom into a nucleophilic species.⁸⁻¹² Stoichiometric carbonyl, or acyl, anions have been traditionally accessed using protected cyanohydrins¹³⁻¹⁶ or metalated dithianes.^{10,17-19} These ap-

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proaches can efficiently construct the desired carbon-carbon bond under strongly basic conditions, but also require postreaction manipulations to unmask the desired carbonyl functionality. In contrast, a number of successful systems have been developed to access carbonyl Umpolung reactivity under catalytic conditions promoted by heteroazolium carbenes.²⁰⁻²³ These highly nucleophilic heterocyclic zwitterions/carbenes possess unique reactivity characteristics and have recently been employed as catalysts for various reactions, including acyl transfer processes,²⁴⁻³⁰ isocyanate trimerizations,³¹ the addition of CF₃ anions to aldehydes,³² and the generation of homoenolates.^{33–35} There are two established and mechanistically related reactions that employ catalytically generated carbonyl anions as nucleophiles. The first process involves aldehydes as the electrophile and is called the benzoin reaction.^{23,36–39} The second type of

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addition, called the Stetter reaction, employs conjugate acceptors and produces 1,4-dicarbonyl products.^{40,41} The continued development of these two related reactions has received significant attention recently and offers new opportunities for unconventional synthetic strategies.

Many catalytic benzoin and Stetter reactions utilize aldehydes as the nucleophilic precursor. These approaches can be complicated by the intrinsic high reactivity of the aldehyde because the intermediate carbonyl anion produced during the reaction can undergo addition to the starting aldehyde, thereby affording self-condensation products. A successful strategy to minimize this potential problem is to generate an intramolecular system by tethering the aldehyde functional group to the electrophile.^{42–45} An alternative approach is to utilize a carbonyl anion precursor that does not possess an aldehyde, thus removing this reactive moiety from the reaction completely. The identification and development of such a precursor should consequently provide the opportunity for a general intermolecular carbonyl anion process. In general, this strategy should allow for a broad inclusion of many classes of electrophiles, and the carbonyl anion generated in situ would not compete between addition to the desired substrate and addition to the aldehyde precursor. Our laboratory has recently reported that intermolecular conjugate addition reactions and additions to activated imines with acylsilanes as the carbonyl anion precursors can be catalyzed by thiazolium-derived carbenes.⁴⁶⁻⁴⁸ The use of these siliconbased carbonyl anion precursors avoids self-condensation, and we have demonstrated that acylsilanes undergo 1,2-silyl shifts (Brook rearrangements)⁴⁹⁻⁵¹ in the presence of neutral Lewis bases, which in turn generate competent carbonyl anions. The use of acylsilanes as carbonyl anions is well documented, and this strategy can offer distinct advantages over aldehydes when employing this Umpolung reactivity pattern.⁵²⁻⁵⁸

During our studies with acylsilanes, we initiated an investigation of additional carbonyl anion precursors that would undergo Stetter-type reactions under catalytic conditions and avoid any potential self-condensation problems. Interestingly, the combi-

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nation α -keto acids in the presence of thiamin diphosphatedependent enzymes address these criteria well (eq 1). Although the biochemical aspects of these enzymes have been studied extensively, significant potential exists to utilize this process for carbon-carbon bond-forming reactions.^{6,7,59-62} The generation of carbonyl anions in this manner has been applied to both the benzoin and the Stetter reaction. For example, Müller⁶³⁻⁶⁵ and Patel⁶⁶ have separately reported cross-benzoin reactions between α -keto acids and aldehydes catalyzed by various decarboxylase enzymes. In a seminal study, Stetter demonstrated that α -keto acids add to unsubstituted vinyl ketones in organic media catalyzed by thiazolium salts in the presence of an amine base.⁶⁷ These mechanistically related systems provided the impetus for us to initiate a study to fully explore this carbonyl anion strategy in the broadest context possible. In general, the addition of nucleophiles to β -substituted conjugate acceptors is considerably more challenging than adding to related vinyl ketones because they are far less reactive due to steric congestion.⁶⁸ Furthermore, we anticipated that the investigation of this reaction manifold with various classes of conjugate acceptors would expand the synthetic utility of this process. We also predicted that the neutral aqueous environment of the original thiamin-dependent enzymes would ultimately be the best conditions to generate useful carbonyl anions. These buffered catalytic conditions would have the potential to tolerate base- or acid-labile functionality and/or protecting groups that could be present when combining complex and/or sensitive fragments.69-71 We report herein that simple analogues of thiamin diphosphate catalyze the conjugate addition of α -keto salts (2) to α,β -unsaturated 2-acyl imidazoles (3) under neutral aqueous conditions to afford 1,4-dicarbonyl compounds in excellent yield (eq 2).

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Results and Discussion

Our initial investigations focused on combining α -keto acids and thiazolium salts with a conjugate acceptor that would

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Table 1. Investigation of Pyruvic Acid/Sodium Pyruvate as a Carbonyl Anion^a

Ph 🔨		+ Me O A	20 mol% 5 conditions 70 °C	Ph 7	Me / N N (3)
entry	Х	solvent	base	time (h)	yield (%) ^b
1	H (1a)	THF	DBU	24	85
2	Na (1b)	THF	DBU	_	_
3	Na	MeOH	DBU	2	89
4	Na	MeOH/buffer ^c	pH 12.0	12	93
5	Na	MeOH/bufferd	pH 9.4	15	94
6	Na	MeOH/bufferc	pH 7.2	8	92
7	Na	MeOH/buffer ^e	pH 4.8	15	91
8	Na	MeOH/buffer ^c	pH 2.2	_	_
9	Na	MeOH/H ₂ O	_	11	91

^a Reactions performed at 0.5 M with 1.3:1 (v:v) mixture of MeOH and 100 mM phosphate-based buffer solution. ^b Isolated yields after column chromatography. c 100 mM phosphate-based buffer solution. d Pyrophosphoric acid-based buffer solution. e 100 mM acetate-based buffer solution.

ultimately provide synthetically valuable products. At the onset, unsaturated ester, amides, and related conjugate acceptors were not viable substrates under a variety of conditions. Additionally, substrates possessing ester termini complicated later studies under aqueous environments. Consequently, we imposed two key requirements during this search to make the overall transformation valuable: (1) the conjugate acceptor possesses substitution at the β -position, and (2) the products be easily converted into an ester equivalent. Initial studies suggested that unsaturated imidazole substrates were competent conjugate acceptors meeting all of our key requirements.^{72,73} Another attractive feature of these substrates was that they are easily synthesized on a large scale by a simple aldol condensation of 2-acetyl-1-methylimidazole and the corresponding aromatic aldehydes (Scheme 1).

After considerable experimentation using pyruvic acid (1a) and 20 mol % thiazolium salt 5, we observed that α,β unsaturated 2-acyl N-methyl-imidazole (e.g., 3) as the electrophile while using DBU⁷⁴ as the base afforded an excellent yield of the carbonyl anion addition product 7 (Table 1, entry 1). Subsequent studies found that optimization of this mixed Bronsted acid/base system was limited to the β -phenyl substrate (6). For example, substituted β -aryl substrates gave low conversions of the carbonyl addition products when using pyruvic acid and DBU. An operationally simple solution to the Bronsted acid/

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Ph
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 Ph $\stackrel{\circ}{\longrightarrow}$ $\stackrel{\circ}{\longrightarrow}$

base problem was to remove the acidic proton on the α -keto acids by forming the corresponding sodium carboxylates. The use of sodium salts (1b) in methanol created much more robust reaction conditions (Table 1, entry 3) that provided homogeneous reactions conditions. While there are a number of commercially available thiazolium salts with various counterions and substitution around the heterocyclic core, thiazolium 5 was superior in terms of conversion and product yields in aqueous media. Replacing the thiazolium salt with alternative heteroazolium salts as possible catalysts (e.g., imidazolium or triazolium salts) does not afford product, underscoring the delicate balance of reactive components for this process.

Driven by our goal to realize this process under aqueous conditions, DBU was replaced with aqueous pH 12 buffer (Table 1, entry 4). Gratifyingly, the reaction proceeds in excellent yield (93%) in a buffered aqueous methanol solution at 70 °C. The methanol was added initially for solubility purposes, and elevated temperature is necessary to induce the reaction; gas evolution, presumably carbon dioxide, initiates at approximately 63 °C.⁷⁵ Lower temperatures significantly reduce the rate of product formation, and the reaction does not proceed to 100% conversion over extended periods of time. An examination of various phosphate buffers indicated that the overall process is operative at pH 7.2 to afford the desired 1,4-dicarbonyl compound 7 (entry 6). Under these neutral aqueous conditions, only the carboxylate salt (1b) is an effective carbonyl anion, presumably because the absence of the proton keeps the balance of pH within a level that an effective concentration of the thiazolium zwitterion is present. In general, sodium carboxylate α -keto salts preformed the best under our optimized reaction conditions. Surprisingly, the reaction proceeds at pH 4.8 (entry 7) or without any external base (entry 10), although longer times are necessary. Reducing the catalyst loading to 10 or 5 mol % does afford product, but 100% conversion is not achieved.

The possibility of the imidazole ring of the substrate/product acting as an internal base for the reaction was addressed by subjecting trans-chalcone to the same reactions conditions as in Table 1. Interestingly, using sodium pyruvate, 20 mol % thiazolium 5 in MeOH/pH 7.2 phosphate buffer mixture afforded 78% of the 1,4-dicarbonyl compound (Scheme 2). In a second control experiment, DBU was replaced with N-Me-imidazole as the base under the organic media conditions (Table 1, entry 3), and no product was observed.

With these neutral aqueous conditions identified for additions to β -substituted conjugate acceptors, pyruvate (1b) was examined as the acyl nucleophile reagent. Generally, the reaction affords high yields of the corresponding 1,4-diketones when β -aryl substituents are employed (Table 2, eq 4). The process is not affected to an appreciable degree by electron-rich or electron-poor aromatic rings in the β -position. Conjugate acceptors with heterocycles appended in the β -position also work well (entries 9 and 10). Electrophilic substrates with β -alkyl

⁽⁷⁵⁾ Carbon dioxide evolution is observed at 63 °C under the reaction conditions. 10 mol % of the thiazolium salt affords good yields of products, but <100% conversion over 24 h.

Table 2. Catalytic Reactions with Sodium Pyruvate (**1b**) and β -Aryl 2-Acylimidazoles^a

	Me O	20 mol ^e _{ONa} pH 7.2 b	% 5 uffer	O Me
н 💎	N → ⁺ Me N → 1b 0	70 °C, M	еОН В-1	
entry	R	time (h)	yield (%)b	product
1	4-MePh	12	87	8
2	4-MeOPh	11	87	9
3	4-ClPh	7	87	10
4	4-BrPh	20	71	11
5	2-MeOPh	16	87	12
6	2-ClPh	18	95	13
7	2-BrPh	16	89	14
8	2-CF ₃ Ph	18	76	15
9	2-furyl	24	80	16
10	2-thiophene	24	90	17

^{*a*} Reactions performed at 0.5 M with 1.3:1 (v:v) mixture of MeOH and 100 mM phosphate-based buffer solution. ^{*b*} Isolated yields after column chromatography.

Table 3. Reactions with Crotyl-2-acylimidazole Acceptors^a

Me	O Me	Me OX Mol% Conditio 70 °C	5 ns Me	
entry	Х	conditions	time (h)	yield (%) ^a
1	Н	THF, 70 mol% DBU,	26	35
2	Na	30 mol% 5 THF, pH 7.2 buffer, 40 mol% 5	28	23

^a Reactions performed at 0.4 M. ^b Isolated yields after column chromatography.

substituents deliver low levels of 1,4-dicarbonyl products (Table 3, eq 5), and efforts are underway to understand this divergence in reactivity. Under organic solvent conditions (THF, DBU), pyruvic acid adds to the crotyl derived imidazole substrate in only 35% yield. Potentially, the presence of enolizable protons on the electrophilic component of the reaction with DBU upsets the balance of acids and bases in solution. Switching the solvent to THF and pH 7.2 buffer to remove the amine base from solution did not provide an improved yield of the addition product, but instead afforded a lower yield. The use of methanol was avoided because the methanol addition product is isolated in good yield (not shown) with either methanol/DBU or methanol/pH 7 buffer conditions.

We have also explored the impact of structural variations on the carbonyl anion for this process (Table 4, eq 6). Many α -keto acids are commercially available and can be easily converted to the corresponding sodium salts.^{76–78} Generally, alkyl and aryl keto carboxylates work well in this reaction. In some cases (entries 2 and 6), our original organic media conditions (MeOH, DBU, thiazolium salt) provide much higher yields than the buffered aqueous conditions. The reason for this is currently not well understood, although variation in solubilities of substrates and products between 100% methanol and a buffered aqueous/methanol combination may play a role. Currently, keto Table 4. Conjugate Additions of α-Keto Carboxylates^a



^{*a*} See Table 2 for details. ^{*b*} IM = *N*-methyl imidazole. ^{*c*} Performed in MeOH with DBU. ^{*d*} NR = no reaction.

acids with α -branching give low conversions of 1,4-dicarbonyl products, presumably due to steric congestion around the carbonyl carbon. Interestingly, the use of sodium trifluoromethyl pyruvate (Table 4, entry 8) does not afford any appreciable level of product and importantly did not exhibit any CO₂ gas emissions. This α -keto carboxylate is presumably forming a hydrate or hemiketal under the reaction conditions, and this prohibits carbene addition to the ketone.⁷⁹

The heightened reaction temperatures for the transformations above provide good to high levels of products in a minimal time period. However, a survey of altered reaction conditions was conducted to promote the reaction at lower temperatures. It was established in our related studies that the newly formed stereogenic center of the addition products undergoes epimerization under the standard reaction conditions (pH 7.2 buffer, methanol, 70 °C). To investigate the possibility of a stereocontrolled variant of this bond-forming process, a modified approach was investigated. Using unsaturated acylimidazoles 8a and 10a as the conjugate acceptors, a variety of Lewis acids and solvents were screened under a host of reaction conditions. We envisioned that both the acylimidazole substrate and the α -keto carboxylate have coordination sites that could interact with an electron-deficient metal and promote a beneficial effect. While a broad survey of Lewis acids has not been successful to date

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Catalytic Reactions with Pyruvate (1b) in Ethylene Table 5. Glycola



^a Reactions performed at 0.4 M in ethylene glycol at 23 °C. ^b Isolated yields after filtration and water wash.

Scheme 3^a



^a [a] MeOH, DABCO, 78%; [b] morpholine, DMAP, 94%.

in lowering the reaction temperature in these carbonyl anion conjugate additions, a change in solvent from methanol to ethylene glycol allowed the reaction to proceed cleanly and in good yield at room temperature. In these reactions, the dicarbonyl products (8 and 10) precipitate directly from solution and are obtained by a simple filtration followed by washing with water and drying in vacuo. In these cases, the product isolated is >95% pure as judged by ¹H NMR (500 MHz).

Under the full organic media reactions conditions (MeOH, DBU, 70 °C), the 1,4-dicarbonyl products (e.g., 8 and 10) do not precipitate from the solution and most likely undergo reversible interactions with the thiazolium zwitterion/carbene derived from 5. To probe this hypothesis, we conducted the organic reaction conditions on substrate 8a and 10a at 23 °C with and without the addition of the products as an additive (Table 5, eq 6). We observed that product inhibition is occurring under the organic reactions conditions where the products do not precipitate from solution. For example, at all reaction times the conversion of 8a to 8 is higher when no additive (product 8) is in the reaction solution. The rate of product formation in both experiments also slows as the reaction progresses.⁸⁰ This effect can also be explained by product inhibition, and presumably these observations account for the lack of 100% conversion at room temperature. Product inhibition would also explain the requirement of increased reaction temperatures when using methanol and DBU and operative lower temperatures in ethylene glycol where 8 and 10 precipitate from solution. In the latter case when the products precipitate from solution, the carbene catalyst has minimal interactions with the resulting carbonyl groups of the product, and thus limited product inhibition occurs when using ethylene glycol (Table 5, entries 1, 2).

The N-methyl imidazole architecture of the carbonyl addition products allows for smooth access to activated ester reactivity by way of an imidazolium intermediate (Scheme 3). The nucleophilic lone pair on the imidazole ring provides a handle for selective functionalization with activated electrophiles. For example, treatment of diketone 7 with methyl trifluoromethanesulfonate (MeOTf) followed by either methanol or morpholine affords high yields of the methyl ester (26, 78%) or amide (27, 94%), respectively.^{73,81} In these processes, we do not observe



Figure 1. Proposed reaction pathway.

enol ether formation of the pendant ketone moiety or trapping of the activated ester by the ketone to deliver furan heterocycles.

Our proposed reaction pathway is similar to the benzoin-type processes involving thiamine-dependent enzymes (Figure 1). The interaction of a thiazolium zwitterion/ylide (I) generated in situ with an α -keto carboxylate generates tetrahedral intermediate (II). The observation that sodium trifluoropyruvate as the hydrate under aqueous conditions does not undergo nucleophilic additions to electrophiles (Table 4, entry 8) is evidence that the addition to the ketone carbon initiates the catalytic cycle. The loss of carbon dioxide affords the enanamine/carbon nucleophile species III,^{82–85} which in very select cases has been isolated.^{86,87} Our considerable efforts to generate and study this species have not been successful to date. A contributing factor in this pursuit is the potential for **III** to revert to an aldehyde and thiazolium zwitterion I when there are no electrophiles present in solution. This situation is present in the thiazolium-catalyzed benzoin reaction in which the addition of a nucleophilic thiazolium to an aldehyde (giving III) is reversible.^{83,84} Slow gas evolution is observed during these reactions at approximately 60 °C by way of an oil bubbler directly attached to the reaction flask. The interaction of the electron-rich enamine III with the unsaturated electrophile induces carbon-carbon bond formation at the desired β -position. A subsequent deprotonation of the resulting tertiary alcohol IV initiates the formation of the ketone moiety in the product and releases I. Importantly, products arising from the addition of the nucleophilic thiazolium species to the conjugate acceptor are not observed.⁸⁸⁻⁹¹ Further investigations into the generation and determination of the level of reactivity of nucleophilic species such as III are currently ongoing.

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(80) See Supporting Information for details.

Conclusions

In summary, we have developed a robust catalytic carbonyl anion reaction that is fully operative over a broad range of pH values. Under neutral aqueous conditions, the combination of α -keto carboxylates and thiazolium salts produces reactive carbonyl nucleophiles that readily undergo conjugate additions to versatile β -substituted unsaturated 2-acyl imidazoles. The reaction is tolerant of aryl substitution on the conjugate acceptors and accommodates a variety of functionality on the carbonyl anion precursors. When the conjugate acceptor possesses enolizable protons, the reaction affords 1,4-dicarbonyl products, but the isolate yields are currently in the 25-35%range. Typical reaction conditions require heat at 70 °C for efficient conversion to products, and product inhibition is observed in the system. Specialized conditions that promote the precipitation of the products allow for the reaction to afford 100% conversion and high yields at 23 °C. The 1,4-dicarbonyl products can be efficiently converted into esters and amides while avoiding furan formation by activation of the imidazole ring. Mechanistic investigations indicate that loss of carbon dioxide is necessary for the reaction to proceed and that the process can be enhanced by modifying the solvent of the reaction. This study details that α -keto acids and α -keto carboxylates undergo nucleophilic conjugate addition to substituted acceptors efficiently under mild conditions using commercially available thiamin analogues as catalysts. Furthermore, the operation of this process over a wide range of acidities (pH 4-12) can be useful with acid- and base-sensitive substrates as well as reaction methodology that incorporate acid-promoted steps. Current work is focused on developing stereoselective variants of this process and expanding the utility of a-keto acids as carbonyl anion reagents in additional bondforming processes.

Experimental Section

General Procedure for the Thiazolium-Catalyzed Carbonyl Addition to Unsaturated Imidazoles. A screw-capped tube was charged with 3-benzyl-5-(2-hydroxyethyl)-4-methyl-thiazolium chloride (5) (22 mg, 0.08 mmol, 20 mol %), α -keto carboxylate sodium salt (0.72 mmol), and α,β -unsaturated-keto-N-methylimidazole substrate (0.40 mmol). Next, methanol (450 μ L) and pH 7.2 phosphate buffer $(350 \ \mu\text{L}, 100 \text{ mM})$ were added via syringe to the screw-capped tube. The resulting mixture was heated to 70 °C and allowed to stir for the allotted time (8-24 h). Upon 100% conversion of the reaction (as judged by thin-layer chromatography, 90% ether/hexanes), the reaction was cooled to room temperature, diluted with ethyl acetate (10 mL), and transferred to a separatory funnel. Saturated sodium chloride (10 mL), saturated sodium bicarbonate (10 mL), and H₂O (10 mL) were added, and the aqueous layer was extracted with ethyl acetate (3 \times 40 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated in vacuo on a rotary evaporator. The resulting residue was purified by flash column chromatography on silica gel.

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Supporting Information Available: Detailed experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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