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Catalytic Dimerization of Crotonates

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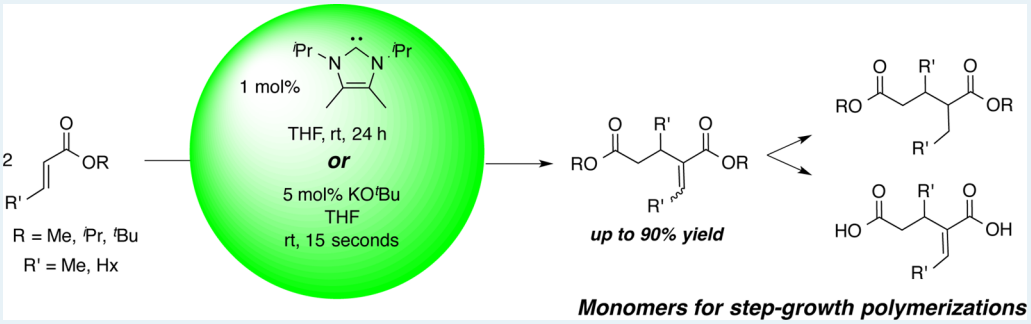
Supporting Information



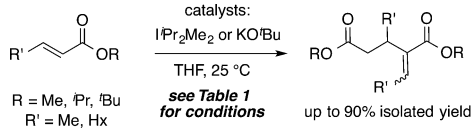
Monomers for step-growth polymerizations

ABSTRACT: A room-temperature dimerization of crotonates into 2-ethylidene-3-methylpentanedioates provides a sustainable route to difunctional monomers for step-growth polymerizations. We report two such dimerizations: (1) an organocatalytic dimerization using the N-heterocyclic carbene 1,3-diisopropyl-4,5-dimethylimidazol-2-ylidene ($I^iPr_2Me_2$) and (2) a rapid dimerization (under 15 s to full conversion) using potassium *t*-butoxide in THF. In addition to unsaturated diesters, the resulting dimers can be easily converted to other step-growth monomers; namely, their corresponding diacids and saturated diesters.

KEYWORDS: *alkenoates, dimerization, N-heterocyclic carbenes, base catalysis, monomer synthesis*

Methacrylates are a versatile class of monomers and chemical intermediates generated on a vast industrial scale. In contrast, the chemistry of the isomeric crotonates is less well-developed; crotonates exhibit chemistry very different from their methacrylate congeners and are not readily polymerized by conventional radical or anionic methods. Both methacrylates and crotonates are currently generated from petrochemical feedstocks. Recently, a new, renewable source of crotonic acid has emerged through the catalytic pyrolysis of the biopolymer poly(3-hydroxybutyrate) (PHB).[1−3] PHB is produced by a variety of microorganisms, including methanotrophic bacteria that can be cultured from wastewater.[4,5] Thus, the generation of crotonate from PHB provides a potential strategy for generating C4 feedstocks from renewable resources, including wastewater streams.[1−3] These breakthroughs in biotechnology motivate the development of new catalytic transformations of crotonate as a potentially renewable C4 feedstock.

The catalytic dimerization of crotonates and alkenoates provides an expedient synthesis of saturated or unsaturated substituted diesters. Although a variety of catalysts for the dimerization of crotonates have been reported, they generally afford poor to moderate yields and require relatively high catalyst loadings at elevated temperatures.[6−10] The dimerization of cyclohexyl crotonate with 25 mol % KO^{t}Bu in a 3:7 DMSO/toluene mixture, proceeded to only 29% conversion after 27 h.[8] The dimerization of ethyl crotonate with 22 mol % $[NBu_4][SiPh_3F_2]$ in THF at room temperature afforded a 74% yield of ethyl 2-ethylidene-3-methylpentanedioate after 2 h,[11] but dimerization with $P[N(CH_3)_2]_3$ required more forcing conditions (300 MPa, 50 °C, 24 h).[12] Fe catalysts, such as 1−5 mol % of $FeH_2(dmpe)_2/h\nu$ or $FeNpH(dmpe)_2$ (dmpe = 1,2-bis(dimethylphosphino)ethane, Np = 2-naphthyl) generate (*E*)-2-ethylidene-3-methylpentanedioates selectively with yields of 73−95% in neat crotonate at room temperature.[13] Herein, we report two facile and selective dimerization reactions of crotonates and alkenoates to 2-alkylidene-3-alkylpentanedioates eq 1.



(1)

Initial attempts to effect the group transfer polymerization (GTP) of isopropyl crotonate with N-heterocyclic carbenes (NHCs)[14−17] in the presence of silyl ketene acetals were unsuccessful; under conditions for the GTP of methyl methacrylate with 1-methoxy-2-methyl-1-(trimethylsiloxy)-propene (MTS)/ 1,3-diisopropyl-4,5-dimethyl-imidazol-2-yli-

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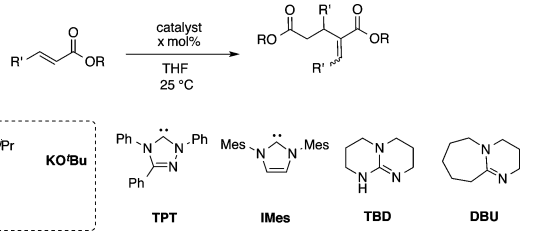
dene ($I^iPr_2Me_2$) to occur readily,[14] no conversion of isopropyl crotonate was observed (see the Supporting Information). In contrast, in the absence of the silyl ketene acetal, the dimerization of isopropyl crotonate occurred readily in the presence of 5 mol % $I^iPr_2Me_2$ in THF-d_8, with 99% conversion to diisopropyl 2-ethylidene-3-methylpentanedioate after 2 h (Table 1, entry 1). Dimerization was carried out on a 2 g scale

Table 1. Catalytic Dimerization of Alkenoates[a]



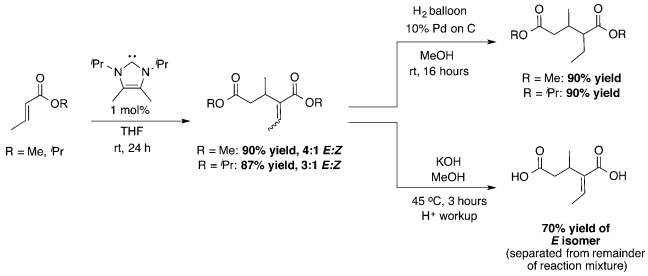
entry	R	R′	catalyst	cat. mol %	time (h)[b]	% conv[c]	ratio E/Z/X[d]
1[e]	^{i}Pr	Me	$I^iPr_2Me_2$	5	2	99	80:20:0
2	^{i}Pr	Me	$I^iPr_2Me_2$	1	24	87[f]	82:18:0
3[e]	Me	Me	$I^iPr_2Me_2$	5	120 s	25	78:22:0
4[e]	Me	Me	$I^iPr_2Me_2$	5	0.5	89	80:20:0
5	Me	Me	$I^iPr_2Me_2$	1	24	90[f]	83:17:0
6	^{t}Bu	Me	$I^iPr_2Me_2$	5	24	72[f]	68:32:0
7	^{i}Pr	Me	DBU	10	24	0	
8	^{i}Pr	Me	TBD	10	24	6[g]	*g*
9[h]	Me	Me	TPT	10	18	10[g]	*g*
10[e]	Me	Me	IMes	100	24	> 99	*g*
11	Me	Me	KO^{t}Bu	5	15 s	89[f]	80:20:0
12	^{i}Pr	Me	KO^{t}Bu	5	15 s	>99	78:22:0
13	^{t}Bu	Me	KO^{t}Bu	5	15 s	>99	73:27:0
14	Me	Hx	KO^{t}Bu	5	0.5	99	56:11:32
15	Me	Hx	KO^{t}Bu	5	18	94[f]	69:13:18
16	Me	Hx	$I^iPr_2Me_2$	5	2	98	31:23:46

[a]Reactions were carried out at room temperature in a nitrogen atmosphere, with $[alkenoate]_0$ = 1 M. [b]Time in hours unless stated otherwise. [c]Conversions measured by ^{1}H NMR integration. [d]Ratios of *E*/*Z*/X isomers measured by ^{1}H NMR integration; X = Double bond isomers (Supporting Information). [e]Solvent = THF-d_8. [f]Isolated yield of the *E*/*Z*/X mixture. [g]Stoichiometric products; see the Supporting Information. [h]80 °C; toluene-d_8 used as solvent instead of THF.

in THF at an $I^iPr_2Me_2$ loading of 1 mol % to afford two isomers of dimer in 87% isolated yield after 24 h (entry 2). The catalytic dimerizations can be carried out in toluene or DMF or in the absence of solvent (liquid crotonate); however, when the reaction was run neat or in the higher dielectric solvent DMF, oligomeric products were also detected (Supporting Information). Methyl crotonate (4 g scale) and *tert*-butyl crotonate were fully converted to their respective dimers (entries 3−6). The assignment of the structure of the isomeric crotonate dimers as the dialkyl 2-ethylidene-3-methylpentanedioates (*E*:*Z* ratios ∼3−4:1) was achieved by a combination of 2-dimensional ^{1}H NMR spectroscopy, IR spectroscopy, and high-resolution mass spectrometry (Supporting Information). The diesters were hydrolyzed to the corresponding diacids, which enabled isolation of the *E* product (Scheme 1). The dimers could also be converted to the saturated pentanoates in high yields by hydrogenation over Pd/C.

Encouraged by the facile catalytic dimerization of crotonate by the NHC $I^iPr_2Me_2$, we investigated other classes of organic

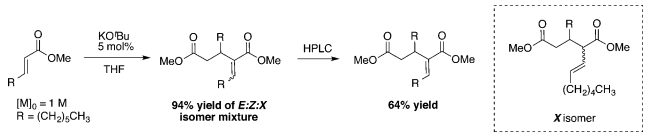
Scheme 1. Conversions of 2-Ethylidene-3-methylpentanedioates



nucleophiles/bases for the catalytic dimerization of crotonate. Several other potent neutral bases/nucleophiles were investigated but did not catalyze the dimerization of crotonate. The amidine 1,8-diazabicycloundec-7-ene (DBU) did not react either stoichiometrically or catalytically with isopropyl crotonate in THF at room temperature (entry 7). The guanidine triazabicyclodecene (TBD), the triazole carbene TPT (TPT = 1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene) and the imidazol-2-ylidene IMes (IMes =1,3-bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene) react stoichiometrically with crotonates to give Michael adducts (entries 8−10, and Supporting Information), but did not mediate any catalytic reactions with crotonates.

However, in light of previous reports,[8] we were surprised to discover that the catalytic dimerization of crotonate with 5 mol % KO^{t}Bu occurred readily at 25 °C in THF; full conversion of methyl, isopropyl, and *tert*-butyl crotonates to the head-to-tail dimer (in similar *E*/*Z* isomeric ratios) occurred in 15 s (Table 1, entries 11−13). The dimer of methyl crotonate was obtained in 89% isolated yield (as a mixture of double bond isomers). The catalytic dimerization of methyl 2-nonenoate with 5 mol % KO^{t}Bu afforded a 94% yield of isomeric 2-heptylidene-3-hexylpentanedioates, from which dimethyl (*E*)-2-heptylidene-3-hexylpentanedioate could be obtained in 64% isolated yield from the nonenoate (entries 14−15). High conversions are observed within 30 min (entry 14), but leaving the reaction for a longer time allowed a higher proportion of 2-alkenoate products to form (entry 15). This reaction represents a particularly mild and rapid conversion of a C9 feedstock to a C18 product (Scheme 2). Although $I^iPr_2Me_2$ is quite effective,

Scheme 2. KO^{t}Bu-Catalyzed Dimerization of Methyl 2-Nonenoate



the use of catalytic KO^{t}Bu provides an operationally straightforward and facile strategy for these dimerization reactions that is a considerable improvement over previous literature reports.[6−13]

The crotonate dimers observed are characteristic of those expected from a Rauhut−Currier reaction, a vinylogous Morita−Baylis−Hillman reaction typically mediated by nucleophilic catalysts.[18−20] Notably, the head-to-tail dimerization of crotonates with N-heterocyclic carbenes occurs with a different regioselectivity from the tail-to-tail dimerization typically observed in the NHC-catalyzed dimerization of methacrylates

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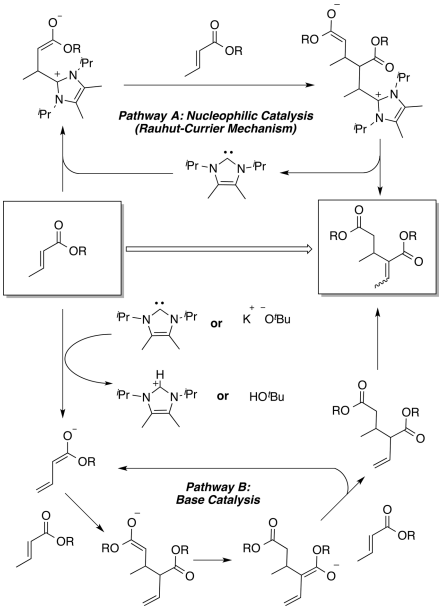
or acrylates.[21−27] Because the regioselectivity of crotonate dimerization with NHCs differs from that of the corresponding acrylates and methacrylates,[21−25] we carried out several experiments to probe the mechanism of the NHC-catalyzed dimerizations. Two plausible mechanistic pathways can be envisaged for catalytic dimerization of crotonates by $I^iPr_2Me_2$: (1) a nucleophilic mechanism (Scheme 3, pathway A: analogous to that proposed for the Rauhut−Currier reaction) or (2) a base-catalyzed reaction mediated by homoenolates (Scheme 3, pathway B).

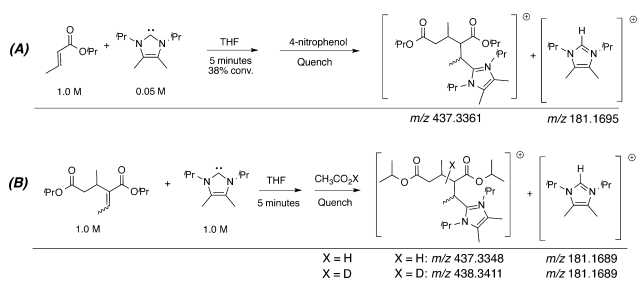
Scheme 3. Catalytic Crotonate Dimerization[a]



[a]Pathway A, nucleophilic catalysis; pathway B, base catalysis.

To assess the potential contribution of a nucleophilic pathway, the reaction of crotonate with $I^iPr_2Me_2$ in THF was monitored by electrospray ionization mass spectrometry (ESI−MS). The ESI−MS spectrum of a crude reaction mixture of 1 M isopropyl crotonate with 5 mol % $I^iPr_2Me_2$ in THF, (quenched after 5 min with 4-nitrophenol) reveals as one of the major species an ion at m/z 437.3361 corresponding to the addition product of $I^iPr_2Me_2$ to the crotonate dimer (formulated as the Michael adduct in Scheme 4A). Fragmentation analysis by tandem mass spectrometry (MS−MS) supports the formulation of this ion as one containing a covalent imidazolium C−C bond because the predominant fragments corresponded to loss of isopropyl groups rather than the imidazolium fragment. Other ions observed include one at m/z 279.1561, corresponding to the sodium adduct of the dimer, and one at m/z 181.1695, corresponding to the protonated imidazolium cation derived from $I^iPr_2Me_2$. No evidence was observed for an ion corresponding to the addition product of $I^iPr_2Me_2$ to isopropyl crotonate.

Scheme 4. Major Ions Observed in ESI−MS from (A) $I^iPr_2Me_2$ + Isopropyl Crotonate and (B) $I^iPr_2Me_2$ + Diisopropyl 2-Ethylidene-3-methylpentanedioate



The formation of the Michael adduct of the crotonate dimer indicates that nucleophilic addition of $I^iPr_2Me_2$ to an α,β-unsaturated enoate is possible, but this evidence by itself is insufficient to rule out a base-catalyzed process by the NHC (Scheme 3, pathway B) as a competitive or even the major pathway for the dimerization. The similar product ratios observed with KO^{t}Bu and the NHC indicate that a base-catalyzed process for both catalysts is plausible. Moreover, the generation of up to 46% of the unconjugated enoate isomer X (defined in Scheme 2) in the dimerization of methyl 2-nonenoate with $I^iPr_2Me_2$ (Table 1, entry 16) is more consistent with a base-catalyzed process than a nucleophilic pathway.

If the NHC catalyzes the dimerization by a base-catalyzed mechanism, this would require that only a fraction of the carbene react with the crotonates to generate the homoenolates (Scheme 3, pathway B); the remaining fraction of the carbene could subsequently add to the dimeric product. To assess this possibility, the crotonate dimer diisopropyl 2-ethylidene-3-methylpentanedioate was treated with a stoichiometric amount of $I^iPr_2Me_2$ for 5 min, followed by the addition of acetic acid (Scheme 4B). The ESI−MS spectrum of this mixture revealed the same ion at m/z 437.3348, along with an ion at m/z 181.1689 corresponding to $I^iPr_2Me_2\underline{H}^+$, the imidazolium cation of $I^iPr_2Me_2$. Moreover, if this latter experiment was repeated with the addition of CH_3CO_2D after 5 min, an ion at m/z 438.3411 was observed that corresponds to the imidazolium adduct of the dimer (Scheme 4B) bearing a single deuterium atom. Significantly, the major ion corresponding to the imidazolium cation was observed at m/z 181.1689. The peaks at m/z 182.1744 ($I^iPr_2Me_2\underline{D}^+$, generated by deuteroquenching of remaining free carbene) and m/z 438.3411 (generated by deuteroquenching of a carbene-dimer addition product) were both only 4% the intensity of the $I^iPr_2Me_2\underline{H}^+$ peak (Supporting Information for full spectra). Control experiments indicate that H/D exchange of the imidazolium ions does not occur to any significant extent on the time scale of these reactions (Supporting Information).

In summary, mechanistic studies and ESI-monitoring experiments provide clear evidence that both nucleophilic and base-catalyzed pathways are viable mechanisms for the dimerization of crotonates by $I^iPr_2Me_2$. Although the available data do not allow us to rule out either pathway unambiguously, the preponderance of evidence is, in our opinion, most consistent with a base-catalyzed process. Nevertheless, it is possible that both processes occur competitively.

This head-to-tail dimerization of crotonates can now be added to the diverse and growing set of catalytic and stoichiometric reactions between NHCs and α,β-unsaturated esters (Scheme 5). Given that we exclusively studied 2-alkenoates to this point, we found it instructive to examine the action of $I^iPr_2Me_2$ with methyl methacrylate (MMA). In contrast to the catalytic dimerization that was observed with crotonates, we instead observed a rapid, stoichiometric dimerization−cyclization (Scheme 5C and Supporting Information). Taton and co-workers recently reported similar behavior when 1,3-diisopropylimidazol-2-ylidene (I^iPr_2) was

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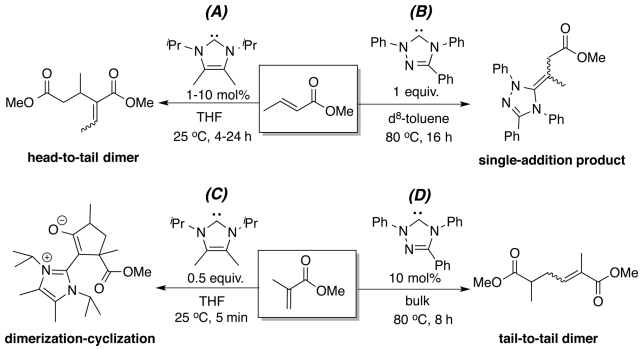
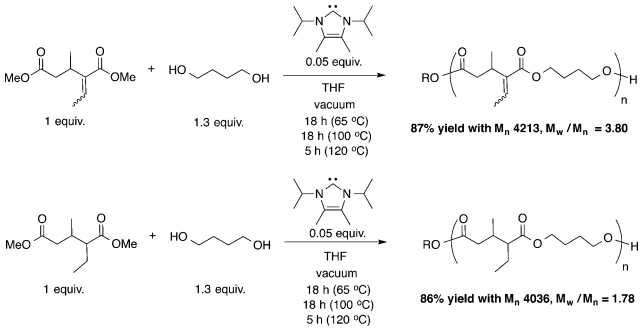
Scheme 5. Reactions of Crotonates (A, B) and Methacrylates (C, D) with $I^iPr_2Me_2$ (A, C) and TPT (B, D)



added to MMA.[17] It is clear that both substrate acidity and electrophilicity play a crucial role in dictating the role of $I^iPr_2Me_2$, which is both a good nucleophile and excellent base.[28] Although methacrylates and crotonates are structural isomers, the difference in the positioning of the vinylic CH_3 results in a large difference in both the acidity of the vinylic CH_3 protons and the electrophilicity of the β carbon of the C=C bond. Whereas the nucleophilicity of $I^iPr_2Me_2$ is the important factor when considering its reactivity with methacrylates, the basicity of $I^iPr_2Me_2$ becomes a crucial additional consideration when assessing its reactivity with the more acidic crotonates and 2-alkenoates.

Because $I^iPr_2Me_2$ is known to act as a transesterification catalyst,[29,30] the generation of novel oligoesters from the crotonate dimers was also examined. Subjecting both the unsaturated and saturated crotonate dimers to 5 mol % $I^iPr_2Me_2$ with a slight excess of 1,4-butanediol resulted in the step-growth production of oligoesters with M_n's of approximately 4000 Da (Scheme 6). The value of M_w/M_n for the

Scheme 6. Oligoester Synthesis via Transesterification Reactions of Crotonate Dimers



unsaturated oligoester was higher (3.80) than for the saturated oligoester (1.78), which may be a consequence of competitive branching reactions of the unsaturated oligomers.

In summary, we have demonstrated that the N-heterocyclic carbene $I^iPr_2Me_2$ is a competent organocatalyst for the dimerization of crotonic acid esters. Furthermore, KO^tBu in THF is an excellent catalytic system for the dimerization of crotonates and provides an expedient route to 2-ethylidene-3-methylpentanedioates. $I^iPr_2Me_2$ can also be employed as a transesterification catalyst in step growth reactions of the dimers to produce novel oligoesters.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b00930.

Synthetic procedures, NMR and mass spectra, mechanistic experiments (PDF)

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Notes

The authors declare no competing financial interest.

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