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COMMUNICATION

Oxidative Rearrangement of Malondialdehyde: Substrate Scope and Mechanistic Insights[†]

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A novel oxidative rearrangement of malondialdehyde was described. Under the effect of H₂O₂, malondialdehyde smoothly transferred to carboxylic acid with C-C bond cleavage in good to excellent yields. Mechanistic studies showed that this reaction proceeded via formation of 1,2-dioxolane intermediate, following by concert C-C, O-O, C-H bonds cleavage and hydride shift.

Baeyer-Villiger oxidation is one of the most important transformations of ketone and aldehyde, which is widely employed in organic synthesis.¹ This reaction provided a regioselective and stereospecific insertion of an oxygen atom to C-C bond to produce ester or lactone (Figure 1). A two-step mechanism has been proposed based on mechanistic studies:² (1) formation of Criegee intermediate II via addition of peroxide to carbonyl; (2) stereospecific skeletal rearrangement of Criegee intermediate to lactone or ester III, which constitutes the rate-determining step. As the second step suffers relatively higher free energy barrier, the Criegee intermediate III could be intercepted by other reaction pathway before it undergoes skeletal rearrangement. In this regard, interrupted Baeyer-Villiger oxidation for formation of 1,2,4-trioxane through cyclization of Criegee intermediate is well documented.³⁻⁶ For example, Criegee intermediate with appendage hydroxyl could transfer to 1,2,4-trioxane via intramolecular acetalization.³ This reaction has been widely employed in synthesis of natural product (e.g. Artemisinin) and pharmaceutical molecules with antimalarial activity.⁴ Criegee intermediate could also be trapped by intramolecular Michael addition to furnish 1,2,4-trioxane when a Michael acceptor is present.⁵ Bloodworth and co-workers developed cyclo-oxymercuration of Criegee intermediate with

tethered alkene followed by reductive demercuration to prepare 1,2,4-trioxane.⁶

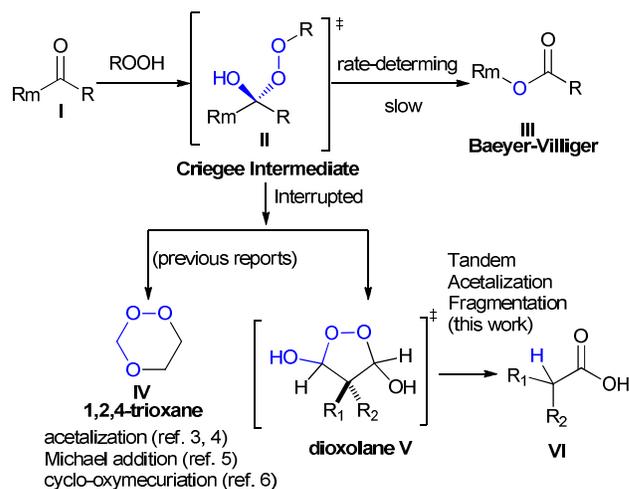
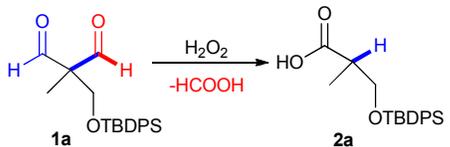


Figure 1 Pathway of Baeyer-Villiger oxidation and interrupted Baeyer-Villiger oxidations.

On the other hand, the removal of functional groups via C-C bond cleavage reactions plays a prominent role in organic synthesis.⁷ Since the first report of the decarbonylation of aldehydes mediated by stoichiometric amounts of Wilkinson's catalyst by Tsuji and Ohno in 1965,^{8a} other reports described the catalytic decarbonylation of aldehydes at 200 °C with Wilkinson's catalyst or other rhodium-based catalysts.^{8b-8c} Still other transition metal-based catalysts including Rh,^{8a-8j} Ru,^{8k} Ir^{8l} and Pd^{8m-8s} proved effective for the catalytic decarbonylation of aldehydes. Mechanistic studies showed that migratory extrusion of CO from metal acyl adduct is the rate-limiting step.^{8j} Although the direct

extrusion of carbonyl group with C-C bond cleavage proved useful in total synthesis,⁹ these decarbonylation procedures suffered from catalyst availability and cost, harsh reaction condition and sometimes, the need for CO scavengers. Herein, we discovered a novel oxidative decarbonylation of malondialdehyde mediated by H₂O₂ that avoided disadvantages of metal catalyzed decarbonylation reactions. The mechanistic studies also supported a tandem acetalization-fragmentation pathway of Criegee intermediate.

Table 1 Reaction condition optimization for oxidative decarbonylation of malondialdehyde **1a**.^a

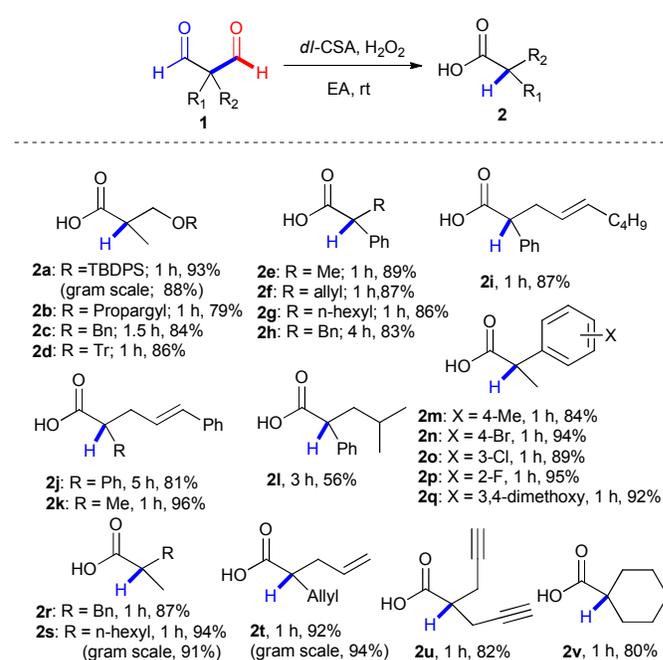


Entry	Catalyst (equiv)	solvent	Time (h)	Yield ^b (%)
1	--	CHCl ₃	5	82(80)
2	PhCOOH (0.1)	CHCl ₃	12	62
3	[(C ₆ H ₅ O) ₂ PO ₃ H (0.1)	CHCl ₃	2	86
4	8H-R-TRIP (0.1)	CHCl ₃	2	65 ^c
5	CF ₃ COOH (0.1)	CHCl ₃	5	72
6	4-CH ₃ (C ₆ H ₄)SO ₃ H (0.1)	CHCl ₃	2	79
7	HCl (0.1)	CHCl ₃	2	60
8	HBFe ₄ (0.1)	CHCl ₃	2	82
9	TfOH (0.1)	CHCl ₃	2	55
10	<i>dl</i> -CSA (0.1)	CHCl ₃	1	91
11	Ag(OTf)	CHCl ₃	12	56
12	Zn(OTf) ₂	CHCl ₃	12	54
13	FeCl ₃	CHCl ₃	12	NR
14	Cu(OTf) ₂	CHCl ₃	6	72
15	<i>dl</i> -CSA (0.1)	EA	1	97
16	<i>dl</i> -CSA (0.1)	MeOH	1	75
17	<i>dl</i> -CSA (0.1)	Acetone	2	86
18	<i>dl</i> -CSA (0.05)	EA	1	97(93)

^a Reaction conditions: malondialdehyde **1a** (0.2 mmol) with H₂O₂ (0.24 mmol) was carried out in the presence of catalytic acid (0.02 mmol) in solvent (2 mL) at rt. ^b NMR yields by using 1,4-dimethoxybenzene as internal standard. Isolated yields are shown in parentheses. ^c 0%ee.

Serendipitously, we found that treatment of malondialdehyde **1a** with H₂O₂ using phosphoric acid as catalyst led to carboxylic acid **2a** as the sole product (Table 1, entry 3). This result was quite unexpected as both aldehydes were oxidized to carboxylic acids along with C-C bond cleavage under mild reaction condition (*vide infra*). Recognizing that this reaction provided quite novel reaction scenario for interrupting Baeyer-Villiger oxidation, we embarked on the reaction condition optimization for this reaction. To our interest, malondialdehyde **1a** smoothly transferred to carboxylic acid **2a** in 82% yield in 5 h even in the absence of any catalyst (Table 1, entry 1). This could be ascribed to be the self-catalyzed effect of the resulting carboxylic acids (*vide infra*). Although phosphoric acid was a good promoter for this reaction, employing chiral phosphoric acid did not lead to any noticeable enantioselectivity (Table 1, entry 4). Subsequently, various Brønsted acids were screened to find a suitable catalyst for this reaction (Table 1, entry 2-10). Carboxylic acids displayed no obvious accelerating effect (Table 1, entry 2 and 5) presumably due to the competitive self-catalyzed effect of

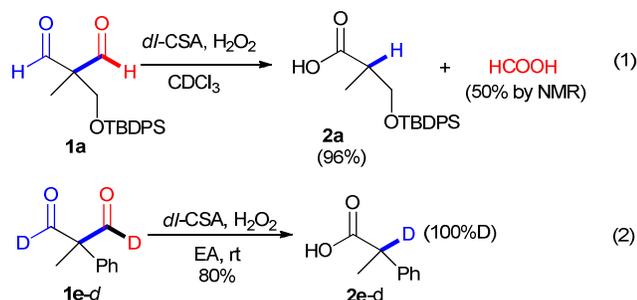
resulting carboxylic acids. In contrast, addition of strong Brønsted acids (e.g. HCl, TfOH, Tf₂NH) gave inferior results owing to lability of malondialdehyde to strong acid. Gratifyingly, camphorsulfonic acid provided optimal result, rendering the reaction completed in 1 h. In sharp contrast, Lewis acids,¹ which facilitate Baeyer-Villiger oxidation using H₂O₂ as oxidant, slowed down the reaction and reduced yields were obtained even after extending reaction time (Table 1, entry 11 to 14). Other reaction condition optimization was also performed. For example, solvent screenings showed that ethyl acetate afforded best isolated yields than any other solvents (Table 1, entry 16, 17 and Supporting Information). Comparable result could be obtained by reducing catalyst loading to 5 mol% (Table 1, entry 18). It should also be pointed out that the reaction is not sensitive to oxygen and moisture, and the reaction could be performed in open flask without rigorous exclusion of water.



Scheme 1 Substrate variation of oxidative decarbonylation of malondialdehyde.

After establishing the optimal reaction condition, various malondialdehydes were prepared and subjected to the standard reaction conditions to test the substrate scope of this reaction. To our delight, most of malondialdehydes smoothly underwent oxidative decarbonylation reaction, leading to carboxylic acid in good to excellent yields in 1 h (Scheme 1). The reaction was found to be somewhat sensitive to steric hindrance and lower yields were obtained for those hindrance-encumbering malondialdehydes (Scheme 1, **2h**, **2j** and **2l**). The reaction conditions were found to be compatible with various protecting groups. Besides the acid-tolerated protecting groups (Scheme 1, TBDPS of **2a** and Bn of **2c**), acid-labile protection group was also found to be intact under the reaction conditions (Scheme 1, Tr of **2d**). 2-Phenyl-malondialdehydes bearing various electron-rich or electron-withdrawing groups were smoothly converted to phenylacetic acids in excellent yields (Scheme 1, **2m-2q**). Easily

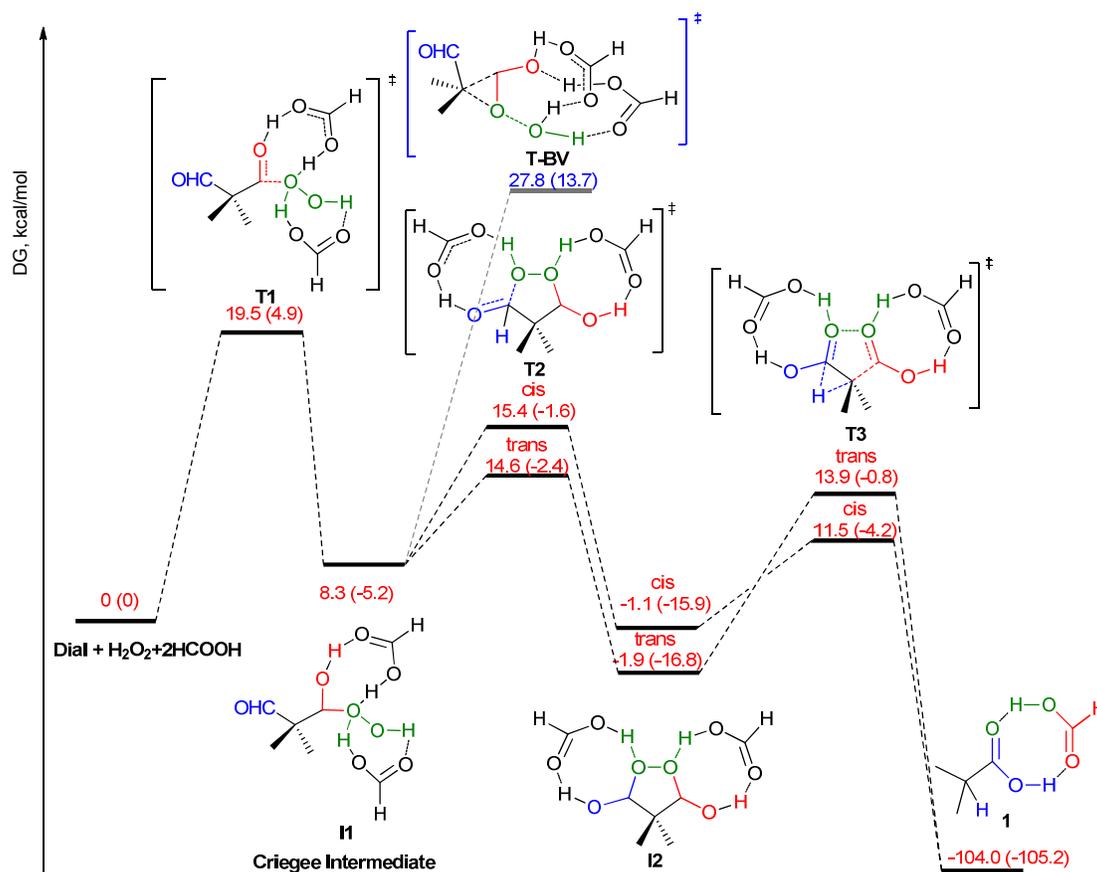
oxidable functionalities such as alkene, alkyne could also survive under the reaction conditions (Scheme 1, **2i-2k**, **2t** and **2u**). Additionally, this reaction was also easily scaled up and carboxylic acid **2b**, **2s** and **2t** could be efficiently prepared in gram scale by following the standard procedure.



Scheme 2 Mechanistic studies of the oxidative decarbonylation reaction.

Although H_2O_2 mediated C-C bond cleavage of 1,3-dicarbonyl compounds has been sporadically reported, mechanistic pathways of those reactions have not been fully

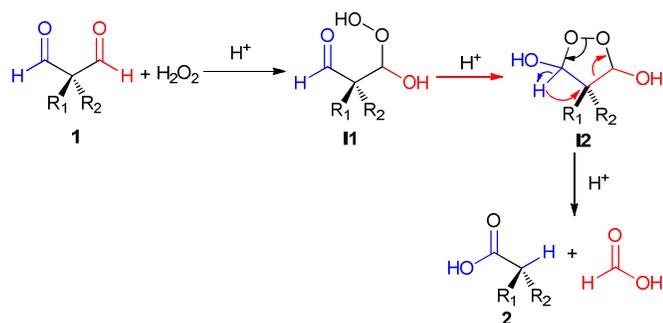
studied to date.¹⁰ To gain insights into the reaction mechanism, the reaction progress was monitored by using ^1H NMR spectroscopy in CDCl_3 (see Supporting Information). The diagram clearly showed that addition of catalytic CSA obviously accelerated the reaction and a self-catalytic effect of resulting carboxylic acids was also observed in the absence of catalyst. Analysis of ^1H and ^{13}C NMR spectra of reaction mixture also revealed the formation of formic acid in 50% yield, implying that both aldehydes were oxidized to carboxylic acids under the oxidative decarbonylation condition (Scheme 2, equation 1). To determine the source of α -proton of the resulting carboxylic acid, deuterated malondialdehyde **1e-d** was also prepared and subjected to the standard reaction conditions (Scheme 2, equation 2). Interestingly, carboxylic acid **2e-d** was obtained with completely deuterated on the α -position as judged by ^1H NMR spectrum, indicating that one of the aldehyde protons shifted to the α -position during the course of oxidative decarbonylation reaction via a concert reaction pathway.



To further elucidate the reaction pathway of the oxidative decarbonylation reaction, DFT calculations at the level of B3LYP/6-31g(d) in the gas phase were also performed by the Gaussian 09 programme.¹¹ As depicted in Figure 2, the calculation showed that unlike Baeyer-Villiger oxidation, the

formation of Criegee intermediate **I1** turned out to be the rate-limiting step of this reaction as transition state **T1** suffered the largest free energy barrier (19.5 kcal/mmol).² Once the Criegee intermediate **I1** formed, it quickly cyclized to 1,2-dioxolane **I2** instead of formation of hydroxyaldehyde through Baeyer-Villiger

transition state **T-BV**, as calculation showed that **T2** (7.1 kcal/mol for *cis*-isomer and 6.3 kcal/mol for *trans*-isomer) suffered much lower free energy barrier than that of Baeyer-Villiger transition state **T-BV** (19.5 kcal/mol). Once relatively stable intermediate **I2** formed, fragmentation of **I2** to carboxylic acids naturally took place as free energy barrier was 12.6 kcal/mol for *cis*-isomer and 15.8 kcal/mol for *trans*-isomer respectively, which could be easily overcome at room temperature. This could also explain why no signal of **I2** was observed on ^1H NMR spectrum of crude reaction mixture at room temperature (see Supporting Information). It's also found by calculation that the fragmentation step was a concert process and transition state **T3** underwent C-C, O-O and C-H bond cleavage with concurrent shift of hydride, which was antiperiplanar to the departure of formic acid (see Supporting Information).



Scheme 3 Proposed mechanism for the oxidative decarbonylation of malondialdehyde.

Based on the mechanistic studies and DFT calculations, we proposed a plausible mechanism for this novel interrupted Baeyer-Villiger Oxidation (Scheme 3). Malondialdehyde **1** reacted with hydroperoxide to give Criegee intermediate **I1** catalyzed by Brønsted acid. Rather than proceeding to the Baeyer-Villiger reaction pathway, Criegee intermediate **I1** spontaneously underwent intramolecular acetalization between peroxide and the other aldehyde to deliver 1,2-dioxolane **I2** with the aid of acid. Eventually, acid catalyzed fragmentation of 1,2-dioxolane **I2** with concurrent cleavage of C-C, O-O and C-H bond and antiperiplanar shift of hydride led to carboxylic acid **2** and formic acid.

Conclusions

In summary, oxidative decarbonylation of malondialdehyde was efficiently achieved in good to excellent yields simply using H_2O_2 as oxidant. Deuterium experiment and DFT calculations showed that capture of Criegee intermediate via intramolecular acetalization with appendage aldehyde followed by concert C-C, O-O and C-H bond cleavage with concurrent migration of hydride was the reaction pathway. Currently, other type of interrupted Baeyer-Villiger oxidation based on tandem acetalization-fragmentation reaction of Criegee intermediate is actively explored in our laboratory.

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Notes and references

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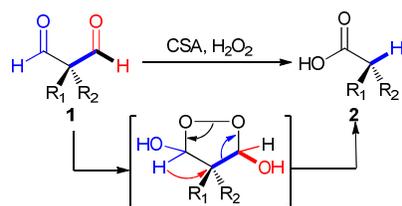
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† Electronic Supplementary Information (ESI) available: General experimental procedures, mechanical studies and spectroscopic data for the all compounds. For ESI or other electronic format See DOI: 10.1039/c000000x/

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11. For detailed information of DFT calculation, see Supporting Information.

Table of Contents



Interception of Criegee intermediate via tandem acetalization and fragmentation reaction provides a novel oxidative decarbonylation of malondialdehyde.