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Decarbonylative Radical Conjugate Addition of Aliphatic Aldehydes for Alkylation of Electron-deficient Alkenes

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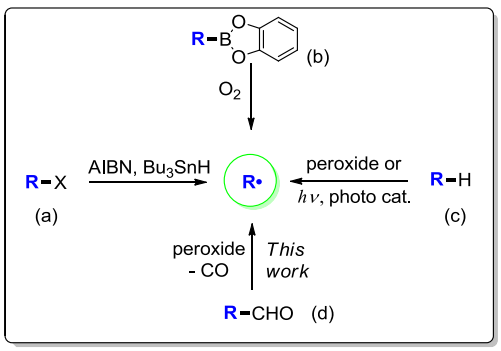
ABSTRACT

A convenient metal-free decarbonylative radical conjugate addition of aliphatic aldehydes to electron-deficient alkenes is developed. With DTBP as an oxidant and radical-initiator, this reaction smoothly converts α-unsubstituted, α-mono-substituted and α-di-substituted aliphatic aldehydes into the corresponding primary, secondary and tertiary alkyl radicals, and subsequently allows for the cascade construction of $C(sp^3)$-$C(sp^3)$ bond via radical conjugate addition.

Introduction

Radical conjugate additions (RCAs) represent a powerful strategy to build up molecular complexity benefiting from the readily availability of alkene feedstock.[1] RCAs frequently proceed under pH-neutral conditions, show a greater functional group tolerance than ionic counterparts and display exceptional chemoselectivity for 1,4- over 1,2-addtion, to make them finding widespread applications in natural products synthesis. [2] However, for the alkylation of electron-deficient alkenes, these utilities have been hampered by limited precursors and laborious procedures for the generation of alkyl radicals. For example, alkyl halides were the most prevalent alkyl radical precursors, but often accompanied by the use of AIBN as radical initiator and toxic tributyltin hydride as halide acceptor (Scheme 1a); [3] while xanthates,[4] B-alkylcatecholboranes[5] and other C-X bonds [1] were also reported as alkyl radical precursors, but the pre-functionalization was necessary (Scheme 1b). Theoretically speaking, alkanes should be the ideal alkyl radical precursors via the direct homolytic abstraction of hydrogen, however, this pathway was limited to symmetric structures existing only one type of sp^3 C-H bond [6a-e] to reduce the possible regioisomers (Scheme 1c), or sp^3 C-H bond adjacent to N/O atoms [6f, g] and other functional groups [6h]. Thus, more convenient methods to provide alkyl radicals with varied structures from readily available sources would be highly desirable.

Aliphatic aldehyde would be such a type of ideal radical precursor for RCAs according to our recent studies on oxidative decarbonylative reactions. With peroxides as radical initiator and oxidant, the decarbonylative couplings of aldehydes with arenes, [7a] heteroarenes,[7b] styrene derivatives,[7c,-e] and the alkylation-cyclization cascade reaction of acrylamides[7f] were successively developed in our group. These decarbonylative reactions were further updated by other groups, with dioxygen as the radical initiator and oxidant. [8] Similarly, the radical type decarbonylative alkylations of aldehydes with C=C and C≡C were developed by Z.-P. Li[9a] and J.-H. Li[9b] respectively. Further, A RCA of aliphatic aldehydes to diaryl alkynoate was reported by Pan *et. al.* to provide the alkylation/arylation product after decarbonylation and decarboxylation cascade. [9c] For the mechanism of these radical type decarbonylative reactions, it's widely accepted that an aliphatic aldehyde was successively transformed into an acyl radical, to provide the corresponding alkyl radical after spontaneous decarbonylation. [7-9] Thus, we postulated that the combination of radical type decarbonylation of aliphatic aldehydes and subsequent conjugate addition to electron-deficient olefins should provide a feasible method for the alkylation of these alkenes.

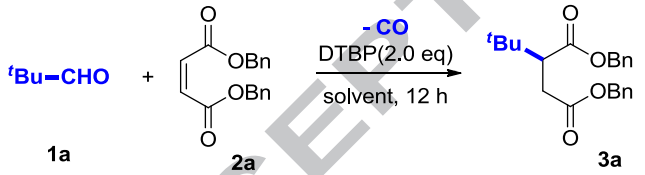


Scheme 1 Various alkyl radical precursors for RCAs.

Results and discussion

Based on our recent studies[7e] and the above mechanistic analysis, we first chose pivaldehyde (**1a**) as the potential radical precursor, and methyl acrylate as the RCA acceptor in the presence of peroxides; which did produce trace amount of RCA product but the polymerization of methyl acrylate was too serious to improve it. So we switched to choose the more electron deficient and structurally symmetric maleate as the RCA acceptor to accelerate the intermolecular radical type nucleophilic addition and suppress the self-polymerization. With dibenzyl maleate (**2a**) used as the RCA acceptor in the presence of TBHP, the decarbonylative RCA of pivaldehyde (**1a**) successfully afforded the desired radical addition product **3a** in 65% yield (Table 1, entry 1). The subsequent optimization revealed that the yields were critically affected by the oxidant used, and the yield raised to 71% with di-*tert*-butyl peroxide (DTBP) added as the oxidant (entry 2); while other peroxides such as dicumyl peroxide (DCP), aqueous hydroperoxide and benzoyl peroxide (BPO) resulted in much lower yields (entries 3–5). Dioxygen was also effective, albeit with only 38% yield. Since the decarbonylation of acyl radical to generate the corresponding alkyl radical requires relatively high temperature, the reaction temperature had an obvious influence on this decarbonylative RCA (entries 7 and 8), and reacting at 130 °C provided the best outcome. Next, the effect of solvent on this oxidative RCA was investigated, and running the reaction in dichlorobenzene (*o*-$C_6H_4Cl_2$) provided the highest yield. The reaction can also be conducted in low polarity solvents such as chlorobenzene and toluene, and more polar solvents such as acetonitrile, DMSO, DMF and NMP (*N*-methyl pyrrolidone), while the low polarity solvents generally provided better yields than the more polar ones (entries 9-15). The usage of 2.0 eq of DTBP was required to realize the full conversion of RCA acceptor (2a), reducing the dosage of DTBP to 1.5 and 1.0 eq resulted in lower yields of 64% and 51%, respectively (entries 16 and 17).

Table 1. Optimization of the oxidative RCA [a]

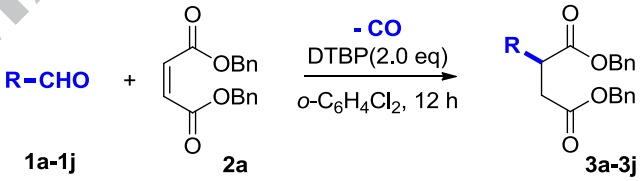


entry	[O]	Solvent	Temp. (°C)	yield [%]
1	**TBHP**	*o*-$C_6H_4Cl_2$	130	65
2	**DTBP**	*o*-$C_6H_4Cl_2$	130	71
3	**DCP**	*o*-$C_6H_4Cl_2$	130	50
4	**H_2O_2**	*o*-$C_6H_4Cl_2$	130	49
5	**BPO**	*o*-$C_6H_4Cl_2$	130	48
6	**O_2**	*o*-$C_6H_4Cl_2$	130	38
7	DTBP	*o*-$C_6H_4Cl_2$	**110**	51
8	DTBP	*o*-$C_6H_4Cl_2$	**150**	57
9	DTBP	**PhCl**	130	67
10	DTBP	**toluene**	130	51
11	DTBP	**CH_3CN**	130	48
12	DTBP	**DMSO**	130	45
13	DTBP	**DMF**	130	9
14	DTBP	**NMP**	130	11
15	DTBP	**dioxane**	130	12
16 [b]	DTBP	*o*-$C_6H_4Cl_2$	130	64
17 [c]	DTBP	*o*-$C_6H_4Cl_2$	130	51

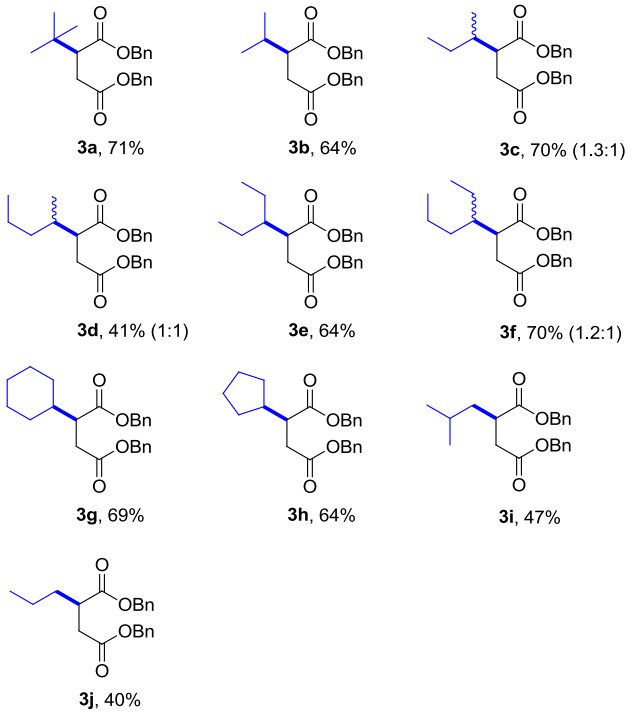
[a] Conditions: **2a** (0.2 mmol), **1a** (0.6 mmol, 3.0 equiv), oxidant (0.4 mmol, 2.0 equiv), solvent (1.0 mL), reacted for 12 h under air unless otherwise noted. Isolated yields. [b] 1.5 eq of DTBP was added. [c] 1.0 eq of DTBP was added.

We next tested the generality of this decarbonylative RCA with different aliphatic aldehydes (**1b**-**1j**) under the optimized conditions (Table 2). While the α-di-substituted pivaldehyde (**1a**) provided tertiary carbon radical after decarbonylation, the α-mono-substituted aliphatic aldehydes including 2-methylpropanal (**1b**), 2-methylbutanal (**1c**), 2-methylpentanal (**1d**), 2-ethylbutanal (**1e**), 2-ethylpentanal (**1f**), cyclohexanecarbaldehyde (**1g**) and cyclopentanecarbaldehyde (**1h**) would provide secondary carbon radicals, which all took part in this decarbonylative RCA to provide the corresponding alkylation product successfully. What's more, the linear (α-unsubstituted) aliphatic aldehydes such as 3-methylbutanal (**1i**) and butanal (**1j**) were also suitable substrate for this reaction, providing lower yields compared with the α-substituted aldehydes, which might be caused by the relatively severer self-aldol condensation of the liner aliphatic aldehydes. It is worth noting that for all of these aliphatic aldehydes tested, no radical rearrangement product was detected, thus proving aliphatic aldehydes as ideal alkyl radical precursors, especially for structurally un-symmetric alkyl radicals.

Table 2. The scope of the aliphatic aldehydes on this decarbonylative RCA [a]

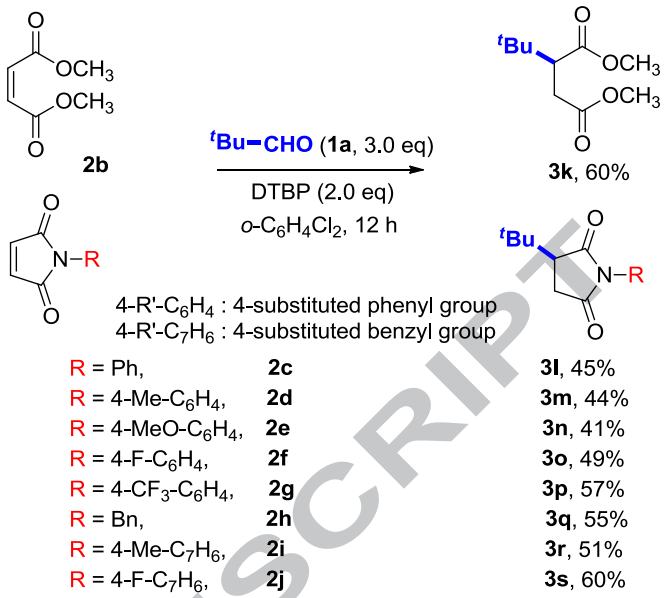


1a	pivaldehyde	**1b**	2-methylpropanal
1c	2-methylbutanal	**1d**	2-methylpentanal
1e	2-ethylbutanal	**1f**	2-ethylhexanal
1g	cyclohexanecarbaldehyde	**1h**	cyclopentanecarbaldehyde
1i	3-methylbutanal	**1j**	butanal



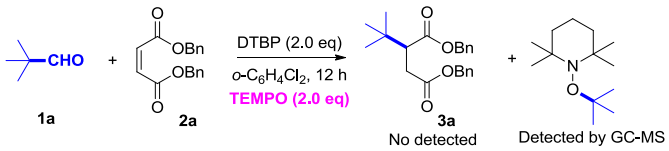
[a] Conditions: **2a** (0.2 mmol), **1** (0.6 mmol, 3.0 equiv), DTBP (0.4 mmol, 2.0 equiv), *o*-$C_6H_4Cl_2$ (1.0 mL), reacted at 130 °C for 12 h under air unless otherwise noted. Isolated yields with the ratio of diastereomers shown in parenthesis.

With the above gratifying results for rather wide substrate scope of aliphatic aldehyde, we next tried different Michael acceptor for this decarbonylative RCA (Scheme 2). Since the forehead mentioned side reaction of self-polymerization, the electron deficient and structurally symmetric maleate was a good choice. Besides dibenzyl maleate (**2a**), structurally similar dimethyl maleate (**2b**) reacted with pivaldehyde (**1a**) to afford the corresponding RCA product in a 60% yield. Furthermore, *N*-phenyl and *N*-benzyl substituted maleimides (**2c**-**2j**) bearing an electron donating (Me, MeO) or withdrawing groups (F, CF_3) at the *para* position of the phenyl ring were turned out to be suitable Michael acceptors for this decarbonylative RCA, which all afforded the corresponding decarbonylative RCA products (**3l**-**3s**) successfully.



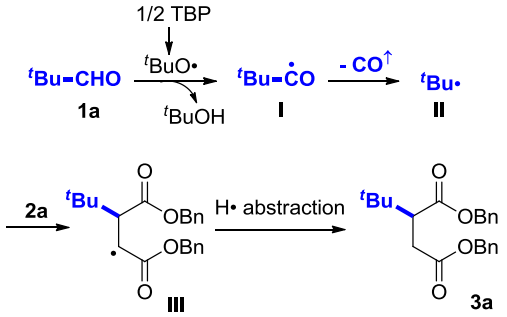
Scheme 2 Maleate and maleimides as Michael acceptor for decarbonylative RCA.

To further understand this decarbonylative RCA of aliphatic aldehydes to electron-deficient alkenes, a mechanistic experiment was carried out in the presence of radical inhibitor. With 2 eq of TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) added, this reaction was completely inhibited and the 1-isopropoxy-2,2,6,6-tetramethylpiperidine was detected by GC-MS (Scheme 3), which not only supported our speculation that the reaction proceeded via a radical pathway but also confirmed the generation of alkyl radical via decarbonylation of aliphatic aldehyde.



Scheme 3 Radical inhibition experiment.

Based on the literature reports [8,9] and our previous studies,[7] a plausible mechanism to understand this decarbonylative RCA was proposed, with the reaction of pivaldehyde (**1a**) and dibenzyl maleate (**2a**) as an example (Scheme 4). First, the homolytic cleavage of DTBP produces *tert*-butoxy radical, which abstracts the aldehyde hydrogen atom to form the pivaloyl radical **I**. Then, the pivaloyl radical **I** undergoes spontaneous decarbonylation to provide *tert*-butyl radical **II**, which readily adds to the electron deficient dibenzyl maleate to generate the radical **III**. Next, a hydrogen abstraction from aldehyde or *tert*-butanol takes place to afford the RCA product **3a**.



Scheme 4 Proposed mechanism for the metal-free oxidative decarbonylative RCA.

Conclusions

We have developed a convenient decarbonylative radical conjugate addition of aliphatic aldehydes to electron deficient alkenes. With DTBP as an oxidant and radical-initiator, this reaction efficiently converted readily available α-unsubstituted, α-mono-substituted and α-di-substituted aliphatic aldehydes into primary, secondary and tertiary alkyl radicals for the RCA. Metal-free conditions, readily availability of aliphatic aldehydes as radical precursor and simple experimental operation for the generation of structurally un-symmetric alkyl radicals would make this strategy attractive for organic synthesis.

Experimental Procedures

An oven-dried reaction vessel was charged with dibenzyl maleate (**2a**, 0.2 mmol, 1.0 equiv), pivaldehyde (**1a**, 0.6 mmol, 3.0 equiv), *o*-dichlorobenzene (1.0 mL) and DTBP (0.4 mmol, 2.0 equiv) under air. The vessel was sealed and magnetically stirred at 130 °C (oil bath temperature) for 12 h. Afterwards the resulting mixture was cooled to room temperature, transferred to silica gel column directly and purified by column chromatography on silica gel with a mixture of EtOAc/petroleum ether as eluent to give products **3a** (50.3 mg, 71 % yield).

Acknowledgments

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The authors declare no competing financial interest.

References and notes

1. For two comprehensive reviews on radical conjugate additions, see: (a) Zhang, W. *Tetrahedron* **2001**, *57*, 7237; (b) Srikanth G. S. C.; Castle, S. L. *Tetrahedron* **2005**, *61*, 10377; (c) Liu, D.; Liu, C.; Lei, A. *Chem. Asian J.* **2015**, *10*, 2040.
2. For the applications of radical conjugate additions in organic synthesis, see: (a) Rowlands, G. J. *Tetrahedron* **2009**, *65*, 8603; (b) Rowlands, G. J. *Tetrahedron* **2010**, *66*, 1593.
3. (a) Studer, A.; Amrein, S. *Synthesis* **2002**, 835; (b) Bowman, W. R.; Storey, J. M. D. *Chem. Soc. Rev.* **2007**,*36*, 1803.
4. (a) Qacemi, M. E.; Petit, L.; Quiclet-Sirea, B.; Zard, S. Z. *Org. Biomol. Chem.* **2012**, *10*, 5707; (b) Zard, S. Z. *Org. Biomol. Chem.* **2016**, *14*, 6891; (c) Beniazza, R.; Liautard, V.; Poittevin, C.; Ovadia, B.; Mohammed, S.; Robert, F.; Landais, Y. *Chem. Eur. J.* **2017**, *23*, 2439.
5. (a) Deng, H.; Wang, D.; Szabó, K. J. *J. Org. Chem*. **2015**, *80*, 3343; (b) Beauseigneur, A.; Ericsson, C.; Renaud, P.; Schenk, K. *Org. Lett*. **2009**, *11*, 3778; (b) Beauseigneur, A.; Ericsson, C.; Renaud, P.; Schenk, K. *Org. Lett*. **2009**, *11*, 3778; (c) Ollivier, C.; Renaud, P. *Chem. Eur. J*. **1999**, *5*, 1468.
6. (a) Narayan, R.; Antonchick, A. P. *Chem. Eur. J*. **2014**, *20*, 4568; (b) Zhao, J.; Fang, H.; Qian, P.; Han, J.; Pan, Y. *Org. Lett*. **2014**, *16*, 5342; (c) Kamijo, S.; Takao, G.; Kamijo, K.; Tsuno, T.; Ishiguro, K.; Murafuji, T. *Org. Lett*. **2016**, *18*, 4912; (d) Kamijo, S.; Kamijo, K.; Maruoka, K.; Murafuji, T. *Org. Lett*. **2016**, *18*, 6516; (e) Zhou, R.; Liu, H.; Tao, H.; Yu, X.; Wu, J. *Chem. Sci*. **2017**, *8*, 4654; (f) Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature*, **2016**, *532*, 218; (g) Chen, R.; Cheng, J.; Yu, J.-T.; *Org. Biomol. Chem*. **2018**, *16*, 1823; (h) Bunescu, A.; Ha, T. M.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed*. **2017**, *56*, 10555.
7. (a) Tang, R. J.; He, Q.; Yang, L. *Chem. Commun*. **2015**, *51*, 5925; (b) Tang, R. J.; Kang, L.; Yang, L. *Adv. Synth. Catal*. **2015**, *357*, 2055; (c) Kang, L.; Zhang, F.; Ding, L.-T.; Yang, L. *RSC Adv.* **2015**, *5*, 100452; (d) Li, Y.-X.; Wang, Q.-Q.; Yang, L. *Org. Biomol. Chem.* **2017**, *15*, 1338; (e) Li, W.; Wang, Q.-Q.; Yang, L. *Org. Biomol. Chem.* **2017**, *15*, 9987; (f) Yang, L.; Lu, W.; Zhou, W.; Zhang, F. *Green Chem*. **2016**, *18*, 2941.
8. (a) Paul, S.; Guin, J. *Chem. Eur. J*. **2015**, *21*, 17618; (b) Biswas, P.; Paul, S.; Guin, J. *Angew. Chem. Int. Ed*. **2016**, *55*, 7756; (c) Kumar, A.; Shah, B. A. *Org. Lett*. **2015**, *17*, 5232.
9. (a) Zong, Z.; Wang, W.; Bai, X.; Xi, H.; Li, Z. P. *Asian J. Org. Chem.*, **2015**, *4*, 622; (b) Ouyang, X.-H.; Song, R.-J.; Liu, B.; Li, J.-H. *Adv. Synth. Catal*. **2016**, *358*, 1903; (c) Pan, C.; Chen, Y.; Song, S.; Li, L.; Yu, J.-T. *J. Org. Chem*. **2016**, *81*, 12065.

Supplementary Material

Electronic Supplementary Information (ESI) available: Experimental details, characterization of products and copies of ^{1}H, ^{13}C NMR.

Highlights

- Abundant aliphatic aldehydes as 1^o, 2^o and 3^o alkyls source
- Simple operations to provide un-symmetric alkyl radicals for RCA radicals
- Metal-free conditions and good functional-group tolerance

Graphical Abstract

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