Trimerization of enones under air enabled by NHC/NaOtBu via a SET radical pathway†

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An unusual trimerization of enone via a formal [2 + 2 + 2] process is disclosed. The reaction is initiated by a radical process enabled by NaOtBu and N-heterocyclic carbene (NHC). Molecular oxygen (air) is involved in key steps of the radical intermediate formation and carbon–carbon bond cleavage in this trimerization reaction to form highly substituted cyclohexane derivatives. In previous studies, alkali metal tert-butoxides such as NaOtBu were mainly employed to generate radical intermediates from aryl halides. Here we provide a new avenue in using NaOtBu and combined NH/NaOtBu to generate radical intermediates from enones for further reactions.

Introduction

Alkali metal tert-butoxides such as NaOtBu or KOtBu have been proved to be good electron donors as pioneered by Stowell in 1981.1 In recent years, NaOtBu or KOtBu has been utilized to generate aryl radicals from aryl halides for coupling reactions with arenes or styrene, as investigated by Shi,2 Shirakawa/Hayashi,3 Lei,4 Studer5 and others (Fig. 1a).6 In these reactions, typically bidentate nitrogen-containing compounds (such as phenanthroline and DMEDA) were used as ligands or additives to enable the single-electron-transfer (SET) processes. In all these reports, aryl radical is suggested as the key intermediate. The generation of aryl radical from aryl halide and addition of the aryl radical to arene or olefin are generally accepted as the key steps.

Here we report a new process mediated by NaOtBu and N-heterocyclic carbene (NHC) for radical reactions of enones that affords unusual trimerization products (Fig. 1b). NHC and NaOtBu were used to enable a SET process that initiates a radical reaction of enone (1a) under air to eventually give intermediate A. Reaction of radical intermediate A with one molecule of enone forms intermediate B that undergoes further reactions with another molecule of enone 1a, leading to trimerization product 3a. Notably, adducts such as 3a could only be prepared from acetophenone and benzaldehyde under harsh conditions in previous reports.7,8 In our process (from A to B), one carbon–carbon bond is cleaved with the release of an aldehyde side product (4) that was experimentally verified. In our present study, N-heterocyclic carbenes (NHCs) were...
used in combination with NaOEtBu to promote the generation of radical intermediates from enones for further reactions. NHCs as organic catalysts were traditionally used in electron-pair reactions. In recent years, NHC-mediated reactions via SET radical processes emerged as a new type of reaction mode for unconventional transformations. Recently, studies from Rehbinder suggested that NHC-mediated benzoin reactions likely go through a radical pathway. 

Results and discussion

We started by using chalcone (1a) as a model substrate (Table 1). When 1a was mixed with 150 mol% NaOEtBu in Et2O for 48 hours, the unconventional trimerization product 3a was obtained in 25% yield (entry 1). The structure and relative configuration of 3a was confirmed via X-ray analysis. We then moved to search for ligands that can improve the reaction. We tested 1,10-phenanthroline previously used in the coupling reactions of aryl halides and arenes, and found the yield of 3a was improved to 59% (see ESI†). At the same time, we found that the addition of 20 mol% imidazolium-based NHC could significantly improve the yield of 3a (80% yield, entry 2). The use of triazolium-based NHCs led to lower yields of 3a (see ESI†). The choice of bases was important for this reaction: KOEtBu was much less effective than NaOEtBu (entry 3); and other typical bases such as NaOH, K2CO3 and Et3N were ineffective (entries 4–7). Reducing the NHC catalyst loading from 20 mol% to 10 mol% led to a slight drop in reaction yield (from 80% to 60% yields, entries 2 and 8). The reaction did not proceed without the presence of base (entry 9). When the loading of base (NaOEtBu) was reduced to 20 mol% (to generate free carbene from the imidazolium salt), no formation of 3a was observed (entry 10). This result (entry 10) suggested that free NHC alone could not mediate this reaction. Replacing Et2O with other organic solvents (such as toluene and CH3CN) led to 3a with moderate to good yields (entries 11–13, and ESI†). As a technical note, “side product” 2a was observed in trace to around 17% yield under our conditions, that might be formed via further reactions of radical anion generated by one electron reduction of chalcone 1a by NHC/NaOEtBu with another two molecules of 1a to give a new trimerized radical anion, which undergoes 6-exo-trig radical cyclization and sequential one electron oxidation to afford 2a (for detailed proposed mechanism for 2a, see ESI†). To the best of our knowledge, the observation of 2a was mentioned in only one report under electrochemical conditions during Fournier’s study on the effect of counter ions for the electroreduction of chalcone.

With an acceptable condition in hand, we evaluated the scope of enones (Table 2) by first varying the aryl substituent next to the carbonyl group. Placing different substituents on this phenyl ring (3b–d) or replacing the phenyl unit with a naphthyl group (3e) were all well tolerated. We then studied the effects of substituents on the β-phenyl group of enone and found that the reactions went smoothly to give corresponding products in moderate to good yields (3f–k). Enones with β-naphthyl or heteroaryl units reacted effectively as well (3l, 3m). Replacing both phenyl units of 1a with other aryl substituents was well tolerated (3n–r).

To gain insights into reaction pathway, we performed several control experiments (Table 3). When 1.0 equivalent of TEMPO was added to the reaction mixture under the standard condition, the yield of 3a dropped from 80% to 16% (entry 1). The formation of 3a was completely suppressed when 3.0 equivalents of TEMPO was added (entry 2). These experiments with TEMPO suggest that our reaction likely go through SET radical pathways. Air is necessary as no reaction occurred when the reaction was performed under N2 (entry 3), supporting the involvement of O2 in our reaction.

Interestingly, when the reaction was carried out under pure oxygen (O2 balloon) (entry 4), no formation of 3a was observed. This can be ascribed to the high concentration of oxygen, as the reduction potential of 1a (−1.85 V vs. Fe/Fe+ (Fc = ferrocene)) was found to be smaller than the that of O2 by approximately 500 mV (reduction potential of O2 is −1.25 V vs. Fe/Fe+). When the reaction was carried out under air, the concentration of 1a was much greater than dissolved molecular oxygen and 1a was able to be reduced by one electron from NHC-NaOEtBu. When the reaction was conducted under
pure oxygen, the dissolved oxygen content would be higher (and be reduced), suppressing the reaction of 1a.

We also conducted electron paramagnetic resonance (EPR) spectroscopic analysis of the reaction mixture of 1a in diethyl ether containing 20 mol% of NHC and 1.5 equivalents of NaOtBu. An exchange broadened and persistent radical signal was obtained at room temperature with a g-value of 2.0050 (Fig. 2), albeit with a low resolution. The EPR spectrum suggests the presence of a radical anion. To further understand the radical intermediate, we conducted cyclic voltammetry studies. Cyclic voltammetry experiments performed on 1a showed that 1a could be reduced at approximately −1.85 V vs. ferrocene 0/+ (Fig. 3). However, the chemical irreversible nature of the voltammetric reduction process indicated that the radical anion form of 1a (intermediate 1 in Scheme 1) could not be the long-lived radical that was detected via the EPR experiments (Fig. 2), as the CV experiments indicate that it is relatively short-lived (lifetime ≪ 1 s). Therefore, the radical anion detected by EPR in Fig. 2 might be intermediate II (Scheme 1), although unambiguous assessment is not feasible at this point.

Based on these mechanistic studies above and results from LC-MS studies (see ESI†), a postulated reaction pathway is illustrated in Scheme 1. The reaction begins with a NHC-assisted release of a electron of NaOtBu\textsuperscript{3,6}c to initiate the reaction.

### Table 2  
**Substrate scope**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Condition</th>
<th>Yield of 3a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Under air, 1.0 equiv. TEMPO</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>Under air, 3.0 equiv. TEMPO</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Degassed, under N\textsubscript{2} atmosphere</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Degassed then connected to O\textsubscript{2} balloon</td>
<td>0 (3 runs)</td>
</tr>
</tbody>
</table>

*Unless otherwise noted, the reactions were conducted in 8 mL vials with 0.2 mmol enones, 20 mol% NHC and 150 mol% of NaOtBu in 3 mL diethyl ether. The reaction mixture was stirred at room temperature (23 °C) under air till the enones were fully converted as monitored by TLC. \textsuperscript{5} Isolated yield. \textsuperscript{6} 0.2 mL THF was added to increase the solubility.

### Table 3  
**Control experiments to elucidate reaction mechanism**

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**Fig. 2** Continuous wave X-band room-temperature EPR spectrum of the reaction mixture of 20 mol% NHC, 1.5 equiv. of NaOtBu and chalcone 1a in diethyl ether. The modulation amplitude = 0.2 G and sweep time = 30 s.

**Fig. 3** Cyclic voltammograms of 5 mM of the analyte recorded at a 1 mm diameter planar circular glassy carbon electrode in acetonitrile containing 0.2 M n-Bu\textsubscript{4}NPF\textsubscript{6} as the supporting electrolyte, at a scan rate of 0.1 mV s\textsuperscript{−1} and at 22 ± 2 °C.
sequent homolytic breaking of the O– radical intermediates

Reaction of undetermined mechanism generates intermediate V. This process is associated with a C–C bond cleavage that leads to an aldehyde adduct (PhCHO).\textsuperscript{22,24} Intermediate 470 | 467


**Conclusions**

In summary, we have developed a NHC/NaO\textsubscript{t} mediated SET to form enone-derived radical anion intermediate that then reacts with molecular oxygen to afford peroxide radical. Subsequent reactions of peroxide radical via the formation of multiple chemical bonds and the cleavage of one C–C bond eventually form multisubstituted cyclohexanes as the enone unusual trimerization products. NaO\textsubscript{t}Bu and similar bases were previously used to generate reactive radical intermediates from aryl halides. Our study provides a new avenue in using NaO\textsubscript{t}Bu and combined NHC/NaO\textsubscript{t}Bu to generate radical intermediates from enones. Further mechanistic studies and design of NHC/alkali metal tert-butoxides for new reaction modes are in progress.

**Acknowledgements**

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**References**

8. 3a is unlikely formed from a reaction of acetophenone and chalcone in our reaction, because acetophenone was not observed (via GC-MS) under our conditions.


One reviewer commented that intermediate IV may undergo HAT process to give β-hydroxyketone, which then goes through retro-aldol reaction and Michael reaction to give intermediate VI. Here, we should state that: (1) it’s hard for intermediate IV to occur HAT process under our reaction conditions, because there is no good hydrogen atom source in the reaction system; (2) the β-hydroxyketone derived from intermediate IV is quite stable, if it really exists, we could have observed (by GC-MS, LC-MS or other method); (3) it’s very hard for such β-hydroxyketone to occur retro-aldol reaction on the basis of literature study, particularly under our reaction conditions.

We could observe the formation of side product aldehyde 4 in our reaction by GC-MS. The aldehyde was finally isolated in its reduced form as benzylic alcohol at the end of the reaction. Unfortunately, the mechanism for the transformation of aldehyde to corresponding benzylic alcohol is currently unclear.