**Tert-Butoxide-Mediated Protodeformylation of Tertiary Homobenzaldehydes**

Xiao Cai and Benjamin J. Stokes†

Department of Chemistry & Chemical Biology, University of California, 5200 N. Lake Road, Merced, CA 95343, USA

Supporting Information Placeholder

**ABSTRACT:** *Tert*-butoxide mediates the protodeformylation of tertiary homobenzaldehydes and related compounds at ambient temperature. Both geminal dialkyl and geminal dialkyl substituents are tolerated. Monocyclic aromatic homobenzaldehydes require cyclic gem-dialkyl or gem-dialkyls for efficient protodeformylation, whereas gem-dimethyls are sufficient for protodeformylation of polycyclic arenyl substrates. Our data suggest a stabilized radical is generated upon attack of the aldehyde by *tert*-butoxide.

The decarbonylation of aldehydes is an important C–C bond-cleaving reaction. Decarbonylations mediated by stoichiometric rhodium complexes at high temperature like the one shown Scheme 1A were first developed by Tsuji and Wilkinson and are notable for their application in natural products total synthesis; flow-type alternatives have been developed to lower the cost. The Haller–Bauer *tert*-butoxide-mediated protodebenzylation has been used as the third step of aldehyde protodeformylation sequences (Scheme 1B). A few other examples of aldehyde decarbonylation have been reported, but have not been generalized.

Herein we describe an ambient temperature *tert*-butoxide-mediated protodeformylation of inherently non-enolizable tertiary homobenzaldehydes and related compounds via a putative stabilized tertiary benzylic radical B generated from unstable *tert*-butoxide adduct A (Scheme 1C). Invoking *tert*-butoxide as a nucleophilic mediator is somewhat uncommon.

In the course of developing new alkene functionalization reactions of tertiary homobenzylstyrenes and related compounds we occasionally observed competing decarbonylation of the precursor tertiary homobenzaldehydes during Wittig olefination if excess *tert*-butoxide was present. We sought to optimize this process using a homonaphthaldehyde substrate (Table 1). Excitingly, 1.6 equivalents of KOt-Bu afforded full substrate conversion and good yield at ambient temperature (entry 1). Solvent evaluation revealed that DMF was also well tolerated (entry 2), while HOt-Bu inhibited the reaction (not shown). Decarbonylation was largely prevented when the reaction was carried out in THF.

**Table 1. Optimization of the Aldehyde Protodeformylation**

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>additive</th>
<th>conv. (%)</th>
<th>yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>KOt-Bu</td>
<td>none</td>
<td>&gt;95</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>KOt-Bu</td>
<td>none</td>
<td>&gt;95</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>KOt-Bu</td>
<td>O₂ (ambient)</td>
<td>&gt;95</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>KOt-Bu</td>
<td>TEMPO</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>KOt-Bu</td>
<td>4 Å mol. sieves</td>
<td>&gt;95</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>NaOt-Bu</td>
<td>none</td>
<td>&gt;95</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>LDA</td>
<td>none</td>
<td>&gt;95</td>
<td>&lt;5</td>
</tr>
<tr>
<td>8</td>
<td>KOH</td>
<td>HOt-Bu</td>
<td>&lt;5</td>
<td>n.d.</td>
</tr>
<tr>
<td>9</td>
<td>KOH</td>
<td>none</td>
<td>&lt;5</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

Reactions were conducted on 0.1 mmol scale in 1.1 mL of solvent under an atmosphere of N₂ unless otherwise noted. Conversions and yields were determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard. N.d. = not detected.

Base formulations unless otherwise noted: KOt-Bu (1.6 M solution in THF); KOH (solid); LDA (2.0 M solution in THF/n-heptane/ethylbenzene); NaOt-Bu (2.0 M in THF). Used solid KOt-Bu and DMF as solvent. Reaction was conducted open to air. Used 100% w/w of molecular sieves. Base and 1.6 equiv of HOt-Bu sonicated for 5 minutes.
was executed open to air, (entry 3) and adding TEMPO inhibited reaction conversion significantly (entry 4). Conversion decreased slightly when molecular sieves were employed (entry 5). NaOEt-Bu was similarly effective (entry 6), but lithium di-iso-propyl amide (LDA) led to decomposition (entry 7). Potassium hydroxide afforded no reaction in aprotic or protic solvents (entries 8 and 9, respectively).

In terms of breadth of scope (Table 2a), phenyl analogs of the naphthyl substrate afford lower yield than the aforementioned naphthyl analog (1a–1c). In particular, 2a is only observed in 11% NMR yield, although the yield can be improved significantly by substituting with a para phenyl group, which affords access to 2d in 67% yield. Strained cyclic gem-dialkyl-containing substrates 1e and a-cyclobutyl (1f) are decarboxylated in just 9% and 24% yield, whereas cyclopropyl (1g) and cyclohexyl (1h) substrates are isolated in useful yield (44% and 76%, respectively). Other monoaryl substrates evaluated include tetralin 1i and triphenylacetaldehyde 1j, both of which undergo decarboxylation in good yield (61% and 79%, respectively).

Compared to many of the examples in Table 2a, fused biaryl substrates afford generally excellent yields (Table 2b), which suggests the reaction may proceed via a benzylic radical intermediate. For example, cyclopentane-containing product 4a is accessed in twice as high a yield as the corresponding monocyclic arene 2g. A 1.0 mmol scale reaction of 1-naphthyl substrate 3b affords the best yield we observed (93% of 4b). 2-Naphthyl analogue 4c is also accessed in good yield, as is 4-substituted benzo[4.5]furan 4d, but 3-substituted benzo[4.5]furan analogue 4e cannot be prepared efficiently; rather, a dearomatized byproduct is formed in higher yield (see below). A number of benzyl-protected indole analogues with the aldehyde linked at the 4-position are also decarboxylated efficiently (3f–3j). Decarboxylation of other heteroaromatic substrates, such as benzo[cyclooctatetraene], is also generally fruitful (4k–4n), except when the aldehyde is linked to the 3-position as in 3o, which may be prone to dearomatization like 3e is.

We also evaluated four fused tricyclic arenes including carbazoles (5a and 5b), a dibenzothiophene (5c), and a dibenzofuran (5d), all of which afford the corresponding decarboxylated products in good yield (Table 2c).

Attempts to trap the putative cleavage intermediate with exogenous electrophiles including Selectfluor®, bromoethane, and D₂O were made, but neither F, nor Br, nor D were incorporated, respectively (see Supporting Information for details). To rule out a canonical decarboxylation, deuterated aldehyde 1d–1i was prepared and afforded a 20% reduction in yield compared to 1d, with no deuterium observed by H NMR at the benzylic position of 2d (eq 1). Employing d₅-THF as a potential trap also yielded no appreciable deuteriation (eq 2).

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**Table 2.** Evaluation of the generality of the tert-butoxide-mediated protodecarboxylation of tertiary aldehydes. a Reactions were conducted on 0.2 mmol of aldehyde (0.09 M in THF) unless otherwise noted, and yields refer to isolated yields unless otherwise noted. b Yield was measured by 1H NMR using 1,3,5-trimethoxybenzene as an internal standard. c Product is volatile under high vacuum. d Reaction was executed on 1.0 mmol scale of 3b.
A hypothetical mechanism is shown in Scheme 1C above, wherein attack by tert-butoxide forms congested intermediate A which may homolyze to give stabilized radical B followed by hydrogen radical abstraction. In addition to the reaction inhibition caused by air and TEMPO (Table 1, entries 3 and 4), support for a radical mechanism is derived from the case of substrate 3e, wherein the alkyl aldehyde is attached to C3 of the benzofuran. In this case, dihydrobenzofuran 7 is isolated as the major product (Figure 2). This kinetic product could manifest as a result of delocalization of the radical onto the oxygen atom (as in D→D'), whereas the corresponding anionic intermediate E is destabilized.

**Figure 2.** Formation of exocyclic alkene byproduct 7 as evidence of a radical mechanism.

In conclusion, we have developed a tert-butoxide mediated protodeformylation of tertiary homobenzaldehydes that may proceed via a stabilized tertiary benzylic radical generated upon homolytic C–C cleavage. Efforts to understand the mechanism in greater detail and to apply the method to selected targets are ongoing.

**ASSOCIATED CONTENT**

Supporting Information. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

**AUTHOR INFORMATION**

**Corresponding Author**

1Current address: Department of Chemistry & Biochemistry, Santa Clara University, 500 El Camino Real, Santa Clara, CA 95053

*bstokes@scu.edu

**Notes**

The authors declare no competing financial interest.

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(16) The preference for heterolytic vs. homolytic cleavage from putative intermediate A is known to be metal-dependent. See: Cram, D. J.; Langemann, A.; Lwowski, W.; Kopecky, K. R. J. Am. Chem. Soc. 1959, 81, 5760.