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Oxidative Decarboxylation of Mandelate Ethers and α-Substituted Phenylacetates via Dioxetanone Generation

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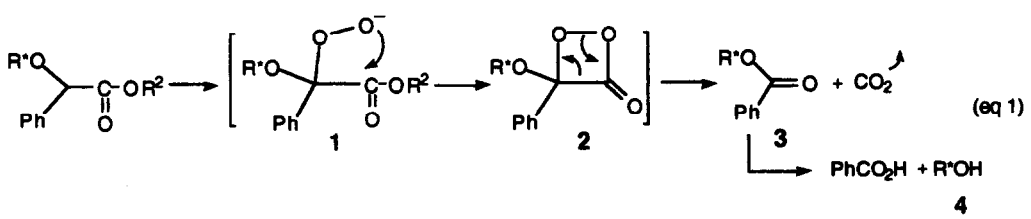
Summary: Mandelate ethers are oxidatively decarboxylated via in situ generated dioxetanones using ^{t}BuOK and air at ambient temperature leading, after hydrolysis, to the benzoic acid and the corresponding alcohol. The reaction can be extended to α-substituted phenylacetates.

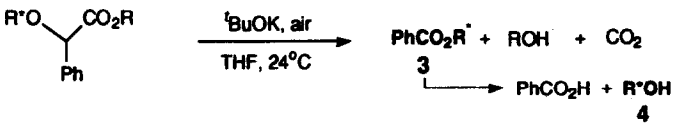
During the course of synthetic studies utilizing 1,3-dioxolan-4-ones for the preparation of chiral secondary alcohols[1], we required a method to convert, under mild conditions, mandelate ethers to the corresponding free alcohols. Literature procedures[2] for related systems utilize the free carboxylic acid and/or harsh reagents, some of which are incompatible with common functionalities. Herein, we describe an efficient and mild oxidative decarboxylation of mandelate ethers via *in situ* generated dioxetanones (eq 1).

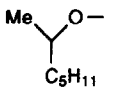
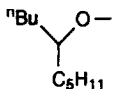
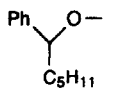
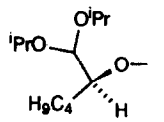
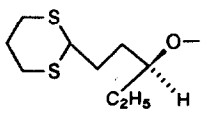
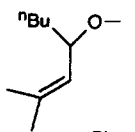
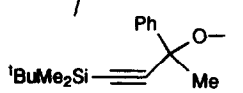


(eq 1)

The reaction was achieved by adding freshly sublimed ^{t}BuOK (1.5 equiv) to a vigorously stirring, room temperature THF solution of mandelate ethers (0.5 - 1 M) open to the atmosphere. Following complete consumption of the starting material (15-30 min), the reaction was quenched with H_2O, extracted thrice with Et_2O, and the combined ethereal extracts concentrated *in vacuo*. Chromatographic purification (SiO_2) of the residue furnished the products from representative examples as summarized in Table 1. The initially generated benzoate (R^1 = O-alkyl) suffered variable degrees of hydrolysis leading to a mixture of benzoate and the corresponding free alcohol[3]. This could be minimized using anhydrous conditions and rapid quenching with sat. NH_4OAc solution or pH 7 buffer. Alternatively, the free alcohol can be easily obtained from the reaction mixture using standard hydrolytic conditions.

Table 1. Decarboxylation of Mandelates ethers



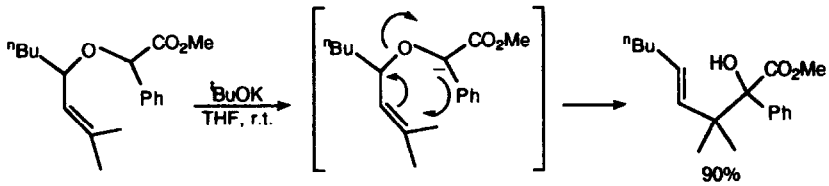
Entry	R*	R	Isolated Yields 3+4 (PhCO$_2$R* / R*OH)
1	MeO–	Me	73% (100 / 0[a])
2		Me	75% (86 / 14)
3		Me	85% (80 / 20)
4		Me	87% (80 / 20)
5		Me	77% (80 / 20)
6		Me	62% (20 / 80)
7	MeO–	menthyl	69% (100 / 0[a])
8		Me[b]	80% (50 / 50)
9		Me[b]	70 % (15 / 85)

[a]No attempt to isolate (4). [b]Anion generated at -78°C then warmed to ambient temperature.

Generally, the identity of the ether had little influence on the outcome of the reaction. Primary (entry 1), secondary (entries 2 and 3), and benzyl (entry 4) ethers afforded good combined yields of (3) and (4).

Importantly, sensitive functionalities such as isopropyl acetal (entry 5) and dithiane (entry 6) were well tolerated and the alcohols were isolated without loss of stereochemical purity[1]. The reaction also readily accommodated esters as bulky as menthyl (entry 7 vs. entry 1).

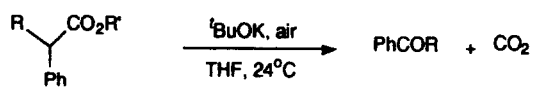
For some unsaturated substituents, however, Wittig rearrangement was competitive under the standard protocol (eq 2). This could be circumvented completely by anion generation at -78°C under an O_2 atmosphere (15 min) followed by warming to room temperature (entries 8 and 9). Quenching the reaction at low temperature afforded the intermediate hydroperoxide corresponding to intermediate (1) which in turn underwent smooth decarboxylation upon re-exposure to the reaction conditions.



(eq 2)

Extension of this procedure to diphenylacetates, Table 2, gave results paralleling those obtained with mandelate ethers.

Table 2. Decarboxylation of α-Substituted Phenylacetates

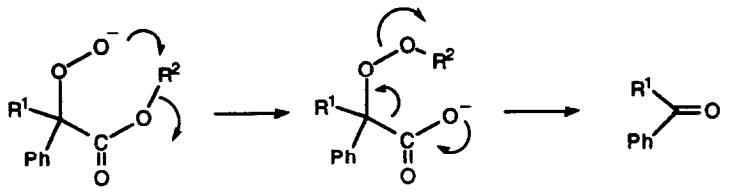


Entry	R	R'	Isolated Yields
1'	Ph–	Me	78 %
2'	Ph–	^{i}Pr	80 %
3'	Ph–	^{t}Bu	78 %

This oxidative decarboxylation is likely to be a general method for the one carbon degradation of α-substituted phenylacetates.

One possible route for the transformation of (1) to the observed products involves intramolecular alkylation of the peroxide anion and subsequent decarboxylation with concomitant peroxide cleavage (eq 3).

This mechanism, however, cannot be reconciled with (a) the reaction's relative insensitivity to steric factors (e.g., entry 10, R^2 = ^{t}Bu) and (b) the recovery of menthol (Table 1; entry 7) rather than the expected inversion product, iso-menthol. More likely, the hydroperoxide anion cyclizes to dioxetanone (2) (α-peroxylactone) which spontaneously decomposes with loss of CO_2 (eq 1). Support for this proposal was obtained by detection of the characteristic chemiluminescence[4] at ~390 nm emitted during the decomposition of dioxetanones in a scanning fluorometer.



(eq 3)

In conclusion, mandelate ethers obtained by addition of magnesio-copper reagents to mandelic dioxolanones[1], can be converted efficiently and under mild conditions, to the corresponding chiral secondary alcohols. The oxidative decarboxylation reaction has also been extended to α-phenylacetates.

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References and Notes

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2. Santaniello, E.; Ponti, F.; Manzocchi, A., *Tetrahedron Lett.*, (**1980**), *21*, 2655-2656.
   Toussaint, O.; Capdevielle, P.; Maumy, M., *ibid.*, (**1984**), *25*, 3819-3822.
   Mashraqui, S.H.; Kellogg, R.M., *J. Org. Chem.*, (**1984**), *49*, 2513-2516.
   Also see, Wasserman, H.H.; Lipshutz, B.H., *Tetrahedron Lett.*, (**1976**), 4613-4616.
3. All new compounds were fully characterized by ^1H /^{13}C NMR and mass spectroscopy.
4. Turro, N.J.; Chow, M.-F., *J. Am. Chem. Soc.*, (**1980**), *102*, 5058-5064.

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