Oxidative Dehomologation of Aldehydes with Oxygen as a Terminal Oxidant

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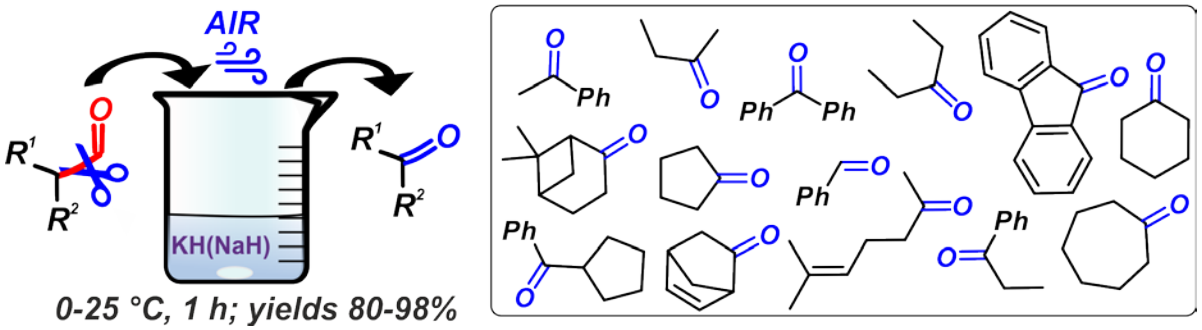
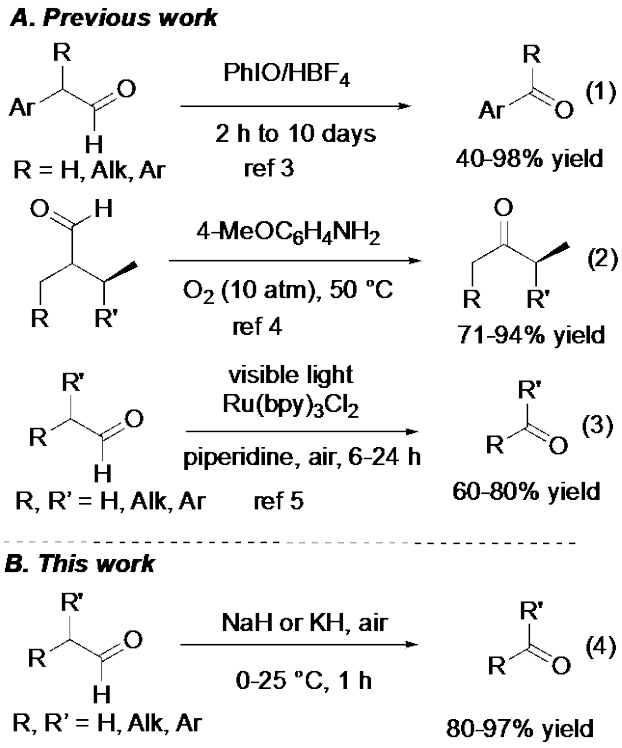
Supporting Information Placeholder



ABSTRACT: A mild, efficient protocol for oxidative cleavage of C-C bond in aldehydes has been developed that employs alkali metal hydrides as reagents and oxygen from air as a terminal oxidant. The method is applicable to a broad substrate range.

Methodologies for efficient and mild cleavage of C-C bonds have a significant synthetic potential. In a specific context, removal of an aldehyde is of a great value because the aldehyde can serve as a temporary activating or directing group in a number of synthetic processes, such as conjugate addition to unsaturated aldehydes or Diels-Alder cycloaddition.[1] Therefore, there is a demand for practical methods for breaking C-C bond in aldehydes with a broad application scope. Commonly, the methods for the oxidative cleavage of aldehydes are based on oxidation of the respective enamines with singlet oxygen or strong oxidants such as periodate or dichromate.[2] However, they require the prior preparation of enamines and are burdened by the formation of undesired side products. More convenient approaches are based on a direct oxidative cleavage of a C-C bond in aldehydes (Scheme 1A). Havare and Plattner[3] used a combination of iodosobenzene with HBF_4 for dehomologation of α-arylaldehydes (reaction 1). This method required long reaction times, while the need for the aromatic group narrowed the scope. Chi and co-workers[4] developed a protocol, where the enamine formed in situ from 4-methoxyaniline and the α-chiral aldehydes was cleaved using molecular oxygen (reaction 2). However, oxygen had to be used at high pressure to drive the reaction to completion. Xia and coworkers reported on oxidative cleavage of C-C bond in aldehydes under conditions of photoredox catalysis using O_2 as a terminal oxidant (reaction 3).[5] In this case, piperidine was used for the in situ formation of enamines. There are other known instances of dehomologation of aldehydes though their scope is limited to single examples.[6]

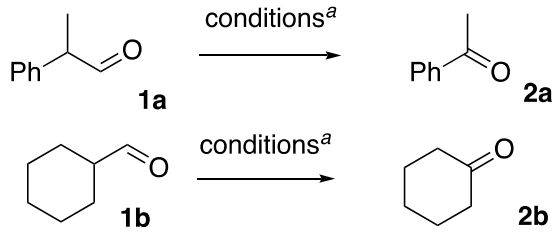
Scheme 1. Strategies for oxidative cleavage of C-C bond in aldehydes.



In this work, we present a mild, facile method for oxidative cleavage of aldehydes that utilizes inexpensive reagents and is applicable to a broad substrate range (Scheme 1B).

While investigating a base-mediated equilibration of diastereomeric α-chiral aldehydes within our program on total synthesis of marine natural products,[7] in some instances we observed loss of the aldehyde group. A more detailed investigation into this process led to development of a convenient practical protocol for the dehomologation of aldehydes.

Table 1. Optimization of cyclization conditions.[a]



entry	substrate	base (equiv)	additive (1 equiv)	conv (%)[b]
1[c]	1a	NaH (1)	-	40
2[c]	1a	KH (1)	-	4
3[c]	1a	KH (1)	18-crown-6	64
4	1a	NaH (1)	-	94
5	1a	KH (1)	18-crown-6	95
6	1a	NaH (0.5)	-	44
7	1a	NaH (1)	dibenzo-18-crown-6	97
8	1a	NaH (1.1)	-	99
9[d]	1a	NaH (1.1)	-	99
10[e]	1a	NaH (1.1)	-	10
11	1b	NaH (1)	-	3
12	1b	NaH (3)	-	7
13	1b	KH (1)	18-crown-6	61
14[c]	1b	KH (1)	18-crown-6	79
15[c]	1b	KH (1.1)	18-crown-6	87
16[c,f]	1b	KH (1.1)	18-crown-6	98

[a]General conditions: substrate (0.1 M solution), base, dry ether. The reactions were performed in air at rt for 1 h, unless stated otherwise. [b]Conversion was calculated from GC. [c]The reaction was carried out at 0 °C. [d]O_2 (1 atm) was used instead of air, the reaction was completed in 30 min. [e]The reaction was carried out under N_2 atmosphere. [f]0.03 M solution of aldehyde in ether was used.

The initial investigation focused on two model substrates, α-arylaldehyde **1a** and aliphatic aldehyde **1b** (Table 1). With **1a**, the use of NaH (1 equiv) at 0 °C in Et_2O after 1 h resulted in a 40% conversion to acetophenone **2a** (entry 1). Under the same conditions, KH produced only traces of **2a** (entry 2). However, the addition of 1 equiv of 18-crown-6 boosted the reaction performance, leading to a 64% conversion to **2a** (entry 3). At rt, with both NaH and KH/18-crown-6, the reactions were essentially completed after 1 h (entries 4 and 5). It was found that the base is required in equimolar quantities, as 0.5 equiv of NaH after 1 h gave only 44% conversion (entry 6). The use of crown ether with NaH did not bring any improvement (entry 7). For the optimal performance, a slight excess of NaH at 1.1 equiv proved to be beneficial (entry 8). Further improvement could be achieved by carrying out the reaction under an atmosphere of pure oxygen (1 atm). In this instance, the reaction time was shortened to just 30 min (entry 9), though otherwise there was not much difference to the reaction in entry 8 that was run in open air. It is important to highlight the crucial role of oxygen in promoting the cleavage, whether it comes from air or is used as a pure reagent. Thus, running the reaction under a nitrogen atmosphere using otherwise identical conditions resulted in a very low conversion (entry 10).

Aliphatic aldehyde **1b** proved to be a more challenging target. The use of NaH gave only traces of product (entry 11). Increasing the amount of base to 3 equiv failed to bring any improvement (entry 12). Promising results were obtained with a KH/18-crown-6 combination. At rt, with 1 equiv of KH, a conversion of 61% was achieved (entry 13), which increased to 79% by lowering the reaction temperature to 0 °C (entry 14). The use of a slight excess of KH (1.1 equiv) brought the conversion to 87% (entry 15). Finally, a complete conversion was attained when a more diluted solution of substrate was employed, 0.03 M compared to 0.1 M in the previous experiments (entry 16). These conditions were taken as optimal for the cleavage of **1b** to **2b**.

Next, the investigation turned to establishing the scope and limitations of the method. The results are presented in Table 2.

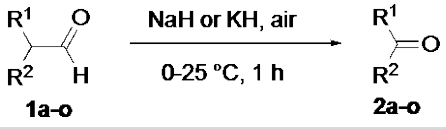
Aldehydes **1c-f** with at least one aromatic substituent in the α-position reacted uneventfully exhibiting similar reactivity to the model substrate **1a**. (entries 1-5). Excellent yields of the respective ketones were obtained using NaH as a base and air as a terminal oxidant. The reactions were complete in under 1 h at rt. However, with phenylacetaldehyde **1g** these conditions proved to be inefficient resulting in a poor conversion. Oxidative cleavage in **1g** could be achieved by replacing NaH by a combination of KH with 18-crown-6, under the conditions developed for aliphatic aldehyde **1b** (Table 1, entry 16), to furnish benzaldehyde **2g** in 80% yield (Table 2, entry 6).

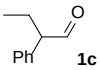
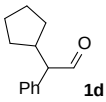
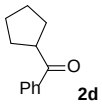
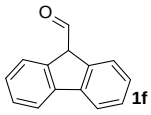
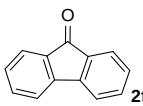
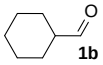
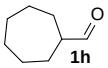
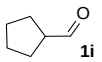
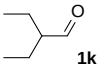
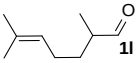
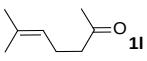
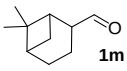
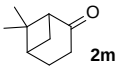
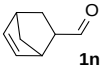
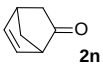
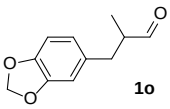
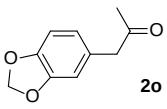
Moving to the aliphatic series and employing conditions from Table 1 entry 16, analogues of **1b** with different ring sizes, such as aldehydes **1h** and **1i**, were successfully converted to the respective ketones **2h** and **2i** (entries 8, 9). It is worth noting that isolation of aliphatic ketones proved to be cumbersome due to their volatility. Therefore, the ketones of the aliphatic series were isolated and characterized as their 2,4-dinitrophenylhydrazones. Acyclic aldehydes **1j** and **1k** exhibited similar reactivity (entries 10, 11), as did terpene derivatives **1l** and **1m** (entries 12, 13).

Aldehyde **1n** is the product of a Diels-Alder cycloaddition between cyclopentadiene and acrolein. The reaction can be carried out enantioselectively where the aldehyde serves as a convenient handle for a chiral catalyst.[8] In the past, conversion of the adducts of type **1n** to ketones like **2n** would require several synthetic steps.[9] Therefore, it was of interest to examine the oxidative dehomologation of **1n**. The reaction proceeded

smoothly yielding ketone **2n** in 85% (entry 14), which represents a considerable shortcut to this valuable synthetic building block.

Table 2. Scope of the Oxidative Cleavage Conditions.[a]



entry	substrate	product	conditions[a]	yields[b] (%)
1	 1a	 2a	A	98
2	 1c	 2c	A	92
3	 1d	 2d	A	91
4	 1e	 2e	A	95
5	 1f	 2f	A	95
6	 1g	 2g	B	80
7	 1b	 2b	B	92[c]
8	 1h	 2h	B	86[c]
9	 1i	 2i	B	84[c]
10	 1j	 2j	B	82[c]
11	 1k	 2k	B	89[c]
12	 1l	 1l	B	84[c]
13	 1m	 2m	B	88[c]
14	 1n	 2n	B	85[c]
15	 1o	 2o	B	32[d]

[a]Reaction conditions: A - aldehyde (1 equiv, 0.1 M in anhydrous Et_2O), NaH (1.1 equiv), air, rt, 1 h; B – aldehyde (1 equiv, 0.03 M in anhydrous $E_{t2}O$), KH (1.1 equiv), 18-crown-6 (1 equiv), air, 0 °C, 1 h. [b]Isolated yield. [c]Yield of the respective 2,4-dinitrophenylhydrazone. [d]Conversion by GC.

Not all the tested substrates reacted well in the oxidative cleavage reaction. Thus, hydrocinnamyl aldehyde **1o** gave a complex product mixture, where, according to the GC-MS analysis, conversion to the desired ketone **2o** was about 32% (entry 15). The reason for this anomalous behavior of **1o** is not clear at the moment.

The reaction mechanism has not been investigated but it is likely to involve formation of the enolate first, followed by autoxidation[10] and intermediate formation of oxetane, analogously to the route proposed for the cleavage of enamines,[4, 11] to furnish ketone **2** and a formate salt of Na or K.

In conclusion, we have developed a mild, facile protocol for an aerobic oxidative cleavage of C-C bond in aldehydes producing the respective ketones. The reaction works well with a wide range of aldehydes. It avoids the use of transition metals catalysts and the only byproduct generated during the reaction is a water-soluble alkali formate.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures; ^{1}H and ^{13}C NMR spectra for new compounds.
The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

The manuscript was written through contributions of all authors.

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