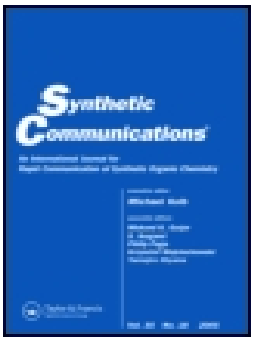

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A Novel Oxidative Aromatic Alkene Cleavage with Sodium Nitrite Under Mild Conditions

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A novel oxidative aromatic alkene cleavage with sodium nitrite under mild conditions

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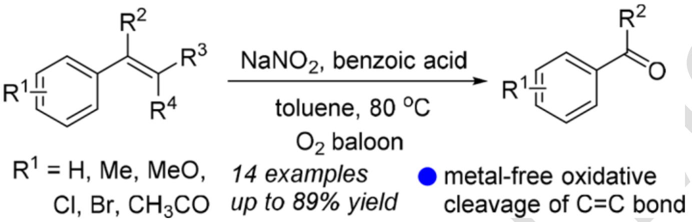
Full experimental details and ^{1}H, ^{13}C NMR and HRMS spectra of other products in the supplementary content of this article web page are available.

Graphical Abstract



We have developed a simple and practical process for the oxidation of aromatic alkene to the corresponding carbonyl compounds by using NaNO$_2$ as an oxidant. The practical utility of this oxidative process has been demonstrated in the gram-scale oxidation of 1-(*tert*-butyl)-4-vinylbenzene.

ABSTRACT

KEYWORDS: aromatic alkene, carbon carbon double bond cleavage, sodium nitrite

Introduction

Alkene oxidation reactions are of fundamental importance in organic synthesis.[1] The oxidative cleavage of alkenes is a synthetically useful transformation in organic chemistry as it allows the oxo-functionalization of olefins. Two main options are available to carry out this reaction chemically: (1) ozonolysis, which presents a major safety concern due to the explosive properties of ozonide intermediates generated,[2] and (2) dihydroxylation followed by oxidative glycol cleavage, which requires toxic high-valent oxometals such as RuO_4 and OsO_4.[3] Milder alternatives relying on hydrogen peroxide or organic hydroperoxides have emerged (traditionally following a radical mechanism), catalysed by Fe(III), Cr(III), Au(I) or V(V) and combined with various ligands.[4] Recently, aryl-λ^3-iodane-based methods for C-C double bond cleavage have been reported.[5] Despite great progress having been made in the field of alkene oxidative cleavage, processes based on inexpensive oxidants are still in high demand.

On the other hand, NO + is a remarkable and diverse reagent, which is commonly applied in nitrosation,[6] nitration,[7] oxygenation,[8] and addition to alkenes to yield oximes, isooxazolines and imidazoles.[9] NO + is also a rather strong one-electron oxidant (1.5 V *vs.* SCE) and this had led to its use in the formation of cation radical intermediates.[10] Using NO + as oxidant, Onomura and co-workers reported the oxidative carbon–carbon (C–C) bond cleavage with $NaNO_2$ in TFA to afford ϖ-amino carboxylic acid in high yield,[11] and Jiang and Wang reported the palladium-catalyzed direct oxidation of alkenes with molecular oxygen. It is well known that NO + could be easily produced by treatment of $NaNO_2$ with a Brønsted acid.

Inspired by these reports and our ongoing interest in the oxidative coupling of indoles using $NaNO_2$ as oxidant,[12] we envisioned that $NaNO_2$ could be applied to the oxidative cleavage of alkenes. Herein, we wish to report the first oxidation of alkenes for the C=C bond cleavage using sodium nitrite as oxidant under mild conditions.

Results and Discussion

To verify the proposed strategy, our initial investigation focused on identifying optimal conditions for the oxidation of styrene **1a** with $NaNO_2$ in the presence of benzoic acid in CH_3CN. To our delight, heating the mixture at 60 °C for 20 h led to oxidative cleavage of styrene and benzaldehyde **2a** was obtained in 39% isolated yield (**Table 1**, entry 1). Encouraged by this preliminary result, we further investigated the reaction parameters and found that the efficiency of the reaction was significantly affected by the choice of solvents.

To begin our investigation, 1-(*tert*-butyl)-4-vinylbenzene (**1a**) was selected as a model system to screen the optimal conditions, and the results are summarized in **Table 1**. First, with the combination of $NaNO_2$ (0.5 equiv) and benzoic acid (0.5 equiv) in CH_3CN at 80 °C under a oxygen atmosphere for 20 h, the desired oxidative product **2a** was obtained in 39% isolated yield (**Table 1**, entry 1). When the reaction was conducted under nitrogen rather than oxygen, no corresponding product was detected. Reactions in acetone left the reactant intact; in sharp contrast, toluene as solvent enabled the oxidative product to a good yield of 70% (**Table 1**, entry 7). Other solvents, such as DMF, DME, 1,4-dioxane, and benzene, showed inferior reactivities (**Table 1**, entries 3-6).

Among the examination of acids, including CF_3CO_2H, TsOH, and HOAc, were inferior to benzoic acid (**Table 1**, entries 8-10). No desired product was observed in a control experiment without the addition of acid (**Table 1**, entry 11). After screening on different parameters, including $NaNO_2$ loadings and temperature (**Table 1**, entries 12-17), the highest yield of **2a** was achieved when the reaction was carried out with $NaNO_2$ (1.5 equiv) and benzoic acid (0.5 equiv) in toluene at 80 °C for 20 h (**Table 1**, entry 14).

With the optimal reaction conditions in hand, we turned our attention to the substrates cope. In general, the reaction proceeded smoothly to give the desired products in good to excellent yields. Substitutions at the C-2, C-3, and C-4 of position of the phenyl ring were all well tolerated. However, aromatic terminal alkenes with electron-rich substituents furnished products with better yield compared with electron-poor counterpart. For example, the 4-OCH_3 substituted substrate gave its product in higher yield than 4-Cl substituted substrate (**Table 2**, entries 4 and 6).

The oxidation of 1,1-disubstituted olefin occurred efficiently to give the ketone in good yield (**Table 2**, entry 11). 1,2-Disubstituted olefins were also subjected to the oxidative cleavage. *cis*-Stilbene and *trans*-stilbene provided benzaldehyde in 83% and 89% yields, respectively (**Table 2**, entries 12 and 13). However, trace of desired oxidative cleavage product was detected when 4-aminostyrene or 4-vinylphenol was subjected to the standard reaction conditions (**Table 2**, entries 14 and 15). In addition, 2-vinylnaphthalene was easily converted to 2-naphthaldehyde in 75% isolated yield. Unfortunately, aliphatic enol, such as but-3-en-1-ol, was not converted to corresponding oxidative cleavage product under the standard reaction conditions.

Finally, the practical applicability of this oxidative cleavage of aromatic olefins is also demonstrated. We used 1-(*tert*-butyl)-4-vinylbenzene as a test substrate and worked on a gram scale. A 50 mmol (8.00 g) reaction of 1-(*tert*-butyl)-4-vinylbenzene was performed with benzoic acid (3.05 g, 25 mmol) and $NaNO_2$ (5.18 g, 75 mmol) in toluene under atmosphere and the mixture was stirred at 80 °C for 20 h. The desired product was obtained in 83% yield. This result indicates that the present approach is a practical process for the oxidative cleavage of aromatic olefins with $NaNO_2$.

Conclusions

In conclusion, we have described a convenient and general procedure for the oxidative cleavage of olefins with sodium nitrite as oxidant. This strategy provides a new avenue for developing C=C bond cleavage under mild conditions. Very importantly, the oxidative system is very easy to handle. Moreover, it has several advantages: (1) the operational simplicity make it potentially useful, (2) a wide variety of functional groups, including electron-rich and electron-withdrawing groups, can survive, (3) this reaction proceeds without exclusion of moisture or air from the reaction mixture.

Experimental Section

General procedure for the preparation of 2

To a solution of alkene (0.3 mmol) and benzoic acid (0.15 mmol) in toluene (1 mL) was added $NaNO_2$ (0.45 mmol) under an air atmosphere and the mixture was stirred at 80 °C for 20-30 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE = 1:8) to yield the corresponding product **2**.

Acknowledgments

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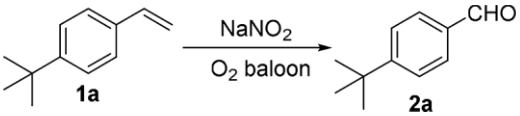
Table 1. Selected optimization of the reaction conditions[a]

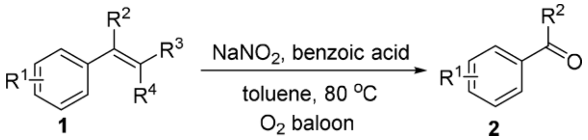


Entry	$NaNO_2$ (equiv)	Acid (equiv)	Solvent	Temp. (°C)	Yield (%)[b]
1	0.5	benzoic acid (0.5)	CH_3CN	80	39
2	0.5	benzoic acid (0.5)	acetone	80	trace
3	0.5	benzoic acid (0.5)	DMF	80	35
4	0.5	benzoic acid (0.5)	DME	80	27
5	0.5	benzoic acid (0.5)	1,4-dioxane	80	43
6	0.5	benzoic acid (0.5)	benzene	80	53
7	0.5	benzoic acid (0.5)	toluene	80	70
8	0.5	CF_3CO_2H (0.5)	toluene	80	19
9	0.5	TsOH (0.5)	toluene	80	25
10	0.5	HOAc (0.5)	toluene	80	37
11	0.5	-	toluene	80	trace
12	1.0	benzoic acid (0.5)	toluene	80	75

13	1.3	benzoic acid (0.5)	toluene	80	78
14	1.5	benzoic acid (0.5)	toluene	80	82
15	1.8	benzoic acid (0.5)	toluene	80	80
16	1.5	benzoic acid (0.5)	toluene	60	36
17	1.5	benzoic acid (0.5)	toluene	100	65

[a] Conditions: **1a** (0.3 mmol), acid (0.15 mmol), and solvent (1 mL), 20 h, under oxygen. [b] Isolated yield.

Table 2. Substrate Scope[a]



Entry	R	Time (h)	Product	Yield (%)[b]
1	R^1 = 4-Bu-*t*, $R^2 = R^3 = R^4$ = H	20	**2a**	82
2	$R^1 = R^2 = R^3 = R^4$ = H	20	**2b**	78
3	R^1 = 4-CH_3, $R^2 = R^3 = R^4$ = H	20	**2c**	81
4	R^1 = 4-OCH_3, $R^2 = R^3 = R^4$ = H	20	**2d**	85
5	R^1 = 2,5-Me_2, $R^2 = R^3 = R^4$ = H	20	**2e**	76
6	R^1 = 4-Cl, $R^2 = R^3 = R^4$ = H	30	**2f**	71
7	R^1 = 2-Cl, $R^2 = R^3 = R^4$ = H	30	**2g**	70
8	R^1 = 4-Br, $R^2 = R^3 = R^4$ = H	30	**2h**	74
9	R^1 = 3-Br, $R^2 = R^3 = R^4$ = H	30	**2i**	72
10	R^1 = 4-$COCH_3$, $R^2 = R^3 = R^4$ = H	30	**2j**	68
11	R^2 = CH_3, $R^1 = R^3 = R^4$ = H	20	**2k**	79
12	R^4 = Ph, $R^1 = R^2 = R^3$ = H	20	**2b**	83

13	R^3 = Ph, $R^1 = R^2 = R^4$ = H	20	**2b**	89
14	R^1 = 4-NH_2, $R^2 = R^3 = R^4$ = H	20	–	trace
15	R^1 = 4-OH, $R^2 = R^3 = R^4$ = H	20	–	trace

[a] Conditions: **1** (0.3 mmol), benzoic acid (0.15 mmol), and $NaNO_2$ (0.45 mmol) in toluene (1 mL), under oxygen. [b] Isolated yield.

Scheme 1. Oxidation of 2-vinylnaphthalene and but-3-en-1-ol.