# <u>Creanic</u> LETTERS

## Transition-Metal-Free Deacylative Cleavage of Unstrained C(sp<sup>3</sup>)– C(sp<sup>2</sup>) Bonds: Cyanide-Free Access to Aryl and Aliphatic Nitriles from Ketones and Aldehydes

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**Supporting Information** 

**ABSTRACT:** A transition-metal-free deacylative  $C(sp^3)-C(sp^2)$  bond cleavage for the synthetically practical oxidative amination of ketones and aldehydes to nitriles is first described, using cheap and commercially abundant NaNO<sub>2</sub> as the oxidant and the nitrogen source. Various nitriles bearing aryl, heteroaryl, alkyl, and alkenyl groups could be smoothly obtained from ketones and aldehydes in high yields, avoiding highly toxic cyanides or transition metals.

he selective cleavage of unstrained C–C bonds has been progressing in recent years.<sup>1–4</sup> The cleavage of unstrained C-C single bonds<sup>2</sup> has always been a critical issue due to its uncontrollable selectivity and inertness compared to the strained C-C bonds such as cyclopropanes with strained small rings or tertiary alcohols with high steric repulsion.<sup>3,4</sup> Transition-metalcatalyzed C-C bond activation has been frequently reported using palladium and copper as catalysts. For example, Murakami and co-workers developed palladium-catalyzed C-C bond cleavage of three to five membered rings.<sup>3</sup> Jiao and co-workers reported copper-catalyzed deacylative C–C bond cleavage under oxidative conditions, patterned in a Bayer-Villager type of oxidative C-C bond cleavage.<sup>2</sup> To date, the deacylative C-C bond cleavaging oxidative amination reaction toward nitriles under transition-metal-free conditions has not vet reported. Nitriles are ubiquitous building blocks in organic synthesis, pharmaceutics (Figure 1), and chemical engineering, as they can be easily transformed into aldehydes, amines, amides,



Figure 1. Nitrile-containing pharmaceuticals.



thioamides, acids, esters, heterocyclic compounds, etc.<sup>5,6</sup> Conventional methods to access nitriles, such as the Sandmeyer and Rosenmund von Braun reactions, were widely employed in the early years.<sup>7</sup> Recently, metal cyanides, metalloid cyanides [MCN (M = Na, K, Zn, Cu), TMSCN, "Bu<sub>3</sub>SnCN, K<sub>3</sub>Fe-(CN)<sub>6</sub>],<sup>8</sup> and organonitriles<sup>9,10</sup> as direct CN sources have also been established. Other methods have also been reported.<sup>11,12</sup> Nevertheless, to the best of our knowledge, no example has been reported to date in which nitriles were directly prepared through C–C bond cleavage from carbonyl compounds under transitionmetal-free conditions. Herein, we report a practical AlCl<sub>3</sub>-promoted oxidative amination of ketones and aldehydes using NaNO<sub>2</sub> via unstrained C(sp<sup>3</sup>)–C(sp<sup>2</sup>) bond cleavage.

Initially, using the oxidative amination of 1-phenyl-2-actone (1a) as a model reaction, different nitrogen sources were selected to optimize conversions (Table 1). Using anhydrous aluminum chloride as the Lewis acid and NaNO2 as the oxidant as well as nitrogen source, 1a was obtained in 90% conversion (entry 1). It was found out that both AlCl<sub>2</sub> and NaNO<sub>2</sub> were necessary for the oxidative amination of 1a to 2a (entries 2 and 3). One advantage for this approach was that the reaction was not air or moisture sensitive and could be run under open air. The reaction under argon atmosphere afforded the same conversion as that under open air (entries 5 and 1), indicating that air was not the oxygen source. Other nitrogen sources such as NaNO<sub>3</sub> and t-BuONO gave much lower conversions (entries 6 and 7). Using ammonium hydroxide as the nitrogen source was not successful (entry 8). The radical trapping agent TEMPO could partially inhibit the reaction (entry 9). Brønsted acids such as acetic acid

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		L. A. [N] (excess) DMF, open air 90 °C, 1.5 h	C≡N 2a	
entry	Lewis acid (equiv)	[N]	atmosphere	$\operatorname{conv}^{\boldsymbol{b}}(\%)$
1	$AlCl_{3}(2)$	NaNO <sub>2</sub>	open air	90
2		$NaNO_2$	open air	0
3	$AlCl_{3}(2)$		open air	0
4	$AlCl_{3}(1)$	$NaNO_2$	argon	53
5	$AlCl_{3}(2)$	$NaNO_2$	argon	90
6	$AlCl_{3}(2)$	NaNO <sub>3</sub>	open air	53
7	$AlCl_{3}(2)$	<i>t</i> BuONO	open air	39
8	$AlCl_{3}(2)$	$NH_3 \cdot H_2O$	open air	0
9 <sup>c</sup>	$AlCl_{3}(2)$	$NaNO_2$	open air	16
10	$AcO_2H(1)$	$NaNO_2$	open air	1
11	TfOH (1)	$NaNO_2$	open air	11
12	$BF_3 \cdot OEt_2$ (1.0)	$NaNO_2$	open air	16

<sup>*a*</sup>Reaction conditions: **1a** (0.5 mmol),  $AICl_3$  (2 equiv), [N] (10 equiv), DMF (0.5 M), 90 °C, open air, 1.5 h. <sup>*b*</sup>Determined by GC using dioxane as the internal standard. <sup>*c*</sup>With 1.6 equiv TEMPO to NaNO<sub>2</sub>. See the Supporting Information for details.

and TfOH and  $BF_3 \cdot OET_2$  fail to promote this reaction (entries 10–12). The conditions described in entry 1 were chosen as the standard conditions for further study.

The scope of this deacylative C-C bond cleavage oxidative amination of ketones and aldehydes to nitriles was then investigated. Aryl and alkyl ketones and aldehydes could be smoothly converted to the desired nitriles (Scheme 1). For example, various aryl and heteroaryl nitriles were obtained in high isolated yields (1b-m). The substrates bearing other carbonyl groups instead of an acetyl group could also give the desired nitriles in high yields (Scheme 1, 1n and 10). Similar to the reaction of 10, both PhCN and MeCN have been detected by GC. Actually, under open air, most MeCN was evaporated. However, acetic acid was also afforded. After workup, only PhCN was isolated in 91% yield. The unstable enone substrate 1p could give the corresponding product in acceptable yield. Besides (hetero)aryl ketones, this method is also suitable for conversion of aliphatic ketones to the corresponding nitriles in high yields (Scheme 1, 1q-t). What should be noted is that aldehydes 1uand 1v were also successfully converted to nitriles.

The kinetic isotope effect (KIE) for 1a is described in Scheme 2. A second-order KIE with a value of 0.7 was found for 1a-D (Scheme 2, top). For the compound 1a'-D, a  $k_{\rm H}/k_{\rm D}$  of 1 was observed. No KIE of 1a-D or 1a'-D indicates the rate-determining step is a C-H cleavage step. Compound 3 was initially hypothesized as a possible intermediate for the conversion to nitrile 2a, and a first-order KIE was observed (Scheme 2, bottom). Another possible intermediate 4a was observed by GC-MS. Compound 4a could not be directly detected by <sup>1</sup>H NMR, whereas 1,2-dione 5a was observed by <sup>1</sup>H NMR. Oxime 4a could be converted to nitrile 2a in 78% yield under standard reaction conditions, but the substrate 1a' bearing an  $\alpha$ -methyl group is difficult to convert to 2a (Scheme 3). Therefore, 4a could be the intermediate in this reaction.

A possible reaction mechanism is proposed in Scheme 4. First, 1a reacts with NaNO<sub>2</sub> and AlCl<sub>3</sub> probably via nitric oxide radical to form intermediate A,<sup>4a</sup> which quickly tautomerized to B. The existence of B is supported by observation of 4a by GC–MS





<sup>*a*</sup>Reaction conditions: 1 (2 mmol), NaNO<sub>2</sub> (10 equiv), AlCl<sub>3</sub> (2.0 equiv), DMF (0.5 M), 90 °C, monitored by TLC; isolated yields. <sup>*b*</sup>120 °C. <sup>*c*</sup>100 °C. <sup>*d*</sup>Determined by GC using dioxane as an internal standard. See the Supporting Information for details.

Scheme 2. Kinetic Isotope Effects



experiments (Scheme 3). Intermediate B transforms to final target nitrile 2a via Beckmann fragmentation.

#### Scheme 3. Control Experiments



Scheme 4. Proposed Mechanism



In conclusion, we have developed a new approach to selective unstrained C–C bond cleavage which provides highly efficient and synthetically practical cyanide-free access to oxidative amination of ketones and aldehydes to nitriles in high yields and wide scope. The use of cheap and commercially abundant  $AlCl_3$  as Lewis acid and  $NaNO_2$  as the oxidant as well as the nitrogen source avoids highly toxic cyanides and expensive transition metals. The mechanistic studies illustrated a possible radical pathway, providing new access to unstrained C–C bond cleavage. Studies on a new type of C–C bond cleavage using this approach are underway in our group.

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03367.

Experimental details and spectroscopic data for all products (PDF)

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#### Notes

The authors declare no competing financial interest.

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