LETTERS

="NH₂OEWG"

Explosive

Shelf-stable

•Easy to handle •Catalytic acid

to use enough

Brønsted Acid Catalyzed Nitrile Synthesis from Aldehydes Using Oximes via Transoximation at Ambient Temperature

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(5) Supporting Information

ABSTRACT: The Brønsted acid-catalyzed synthesis of nitriles is described via transoximation under mild conditions using an *O*-protected oxime as a more stable equivalent of explosive *O*-protected hydroxylamines. The nitrile was generated via an *O*-protected aldoxime produced from the aldehyde and an *O*-protected oxime through transoximation. The reaction could be performed on a 1 g scale.

N itriles are important compounds found in pharmaceut-icals, natural products, polymers, and textiles.¹ The Sandmeyer reaction affords aromatic nitriles from diazo compounds using metal cyanide, and the S_N2 reaction between a halogenated alkane or O-mesylated alcohol and alkali metal cyanides gives aliphatic nitriles. However, these reactions require stoichiometric amounts of highly toxic metal cyanide.² Methodologies for synthesizing nitriles have recently been developed that do not require cyanide compounds, for example, for the ammoxidation of methyl arene³ and alcohol⁴ and the dehydration of aldoxime⁵ and amide.⁶ Inspired by enzymatic synthesis, we have demonstrated the iron-catalyzed dehydration of aldoximes under nitrile-free conditions.⁷ The use of aldehydes as starting materials is highly attractive because aldehydes are commercially available and directly afford nitriles without the need to isolate the oxime. Several nitrogen sources for use with aldehydes include the highly toxic sodium azido used in the Schmidt reaction,⁸ explosive hydroxylamines⁹ and derivatives,¹⁰ and ammonia coupled with transition-metal catalysis or stoichiometric iodine.¹¹ However, few Brønsted acid catalyzed nitrile syntheses from aldehydes at ambient temperature have been reported.¹² The mild conditions required to perform the reaction are also important in the view of safety when explosive compounds are treated.

We recently focused on the transoximase isolated from the pupae of silkworm (Figure 1a)¹³ and developed a Brønsted acid catalyzed transoximation reaction (Figure 1b).¹⁴ In the present research, we demonstrate that the stable oxime is equivalent to explosive hydroxylamine in this reaction. Analysis of the reaction mechanism showed that several nitriles **4a** are obtained when aldehyde **1a** is reacted with ethyl *O*-(4-fluorobenzoyl)-acethydroxamate **2a** (Figure 1c).

Some hydroxylamine derivatives are explosive and unstable,¹⁵ prompting us to propose that a stable *O*-protected oxime could act as the equivalent of unstable hydroxylamine derivatives under catalytic transoximation reaction conditions (Figure 2). Herein, we attempted the Brønsted acid catalyzed synthesis of nitriles from aldehydes via transoximation under mild conditions (Figure 1d).



Ph Brønsted acid 5 mol % R−C≡N

Toward Nitrile

Figure 1. (a) Enzymatic transoximation observed in the pupae of silkworm. (b) Catalytic transoximation. (c) Discovery of formation of nitrile. (d) Catalytic nitrile synthesis from aldehyde via transoximation.



Figure 2. Advantages of using oxime instead of hydroxylamine derivatives.



Starting with transoximation reaction conditions, we optimized the reaction conditions for nitrile synthesis (Table 1). Various oxime protecting groups were tested in the



^{*a*}Reaction conditions for aldehydes: **1a** (0.34 mmol), **2** (1.05 equiv), catalyst (5 mol %) in CH₂Cl₂ (0.50 M, 28 ppm of H₂O measured by Karl Fischer titration was contained) at rt. ^{*b*}Ratio was determined from crude mixtures by ¹H NMR. ^{*c*}Isolated yield. ^{*d*}70 wt % HClO₄ aq was used. ^{*e*}35 wt % HCl aq was used. ^{*f*}81 mg of Amberlyst 15 (200 g/mol) was used. ^{*g*}The parentheses means reaction yield using amberlyst recycled this reaction at 20th times. ^{*h*}MS4 Å (78 mg) was added.

presence of perchloric acid catalyst, and a moderate yield was obtained using O-Ms-oxime 2b (entry 2). To our delight, Obenzenesulfonyl oxime 2c gave nitrile 4a in good yield after a 9 h reaction (entry 3).¹⁶ We next examined various stable catalysts to replace explosive perchloric acid. No reaction occurred in the absence of catalyst or in the presence of TFA (entries 4 and 5). Interestingly, the reaction with highly versatile Brønsted acid (hydrogen chloride, sulfuric acid, methanesulfonic acid, or benzenesulfonic acid and derivatives) as 5 mol % catalyst proceeded smoothly at room temperature (~23 °C) (entries 6-9). TfOH showed reactivity comparable to perchloric acid, and the reaction was complete in 9 h (entry 10). Amberlyst-15 is an excellent heterogeneous catalyst,¹⁷ and we demonstrated for the first time that it gave nitrile 4a in good yield (entry 11). Amberlyst-15 can be recovered by filtration and reused 20 times for the same reaction (Figure S1). In contrast, BF3·Et2O (Lewis acid) did not work as a catalyst for this reaction. TfOH treated with molecular sieves also did not catalyze this reaction, showing that some water is required and it plays a key role in nitrile production, as previously reported for transoximation.¹⁴

Having optimized the reaction conditions, we investigated the utility of various aldehydes (Scheme 1). The reaction proceeded with aromatic aldehydes possessing either an electron-donating or an electron-withdrawing group (4a-n). Heteroaromatic aldehydes were also smoothly converted (4o and 4p), and indole-3-carboxyaldehyde 1q was converted to 3Scheme 1. Scope of Various Aldehydes^{*a,b*}



^{*a*}Reaction conditions for aldehydes: 1 (0.50 mmol), 2c (1.05 equiv), TfOH (5 mol %) in CH₂Cl₂ (0.50 M) at rt. ^{*b*}Isolated yield. ^{*c*}Reaction time: 48 h. ^{*d*}2.1 equiv of 2c was used for terephthalaldehyde 1n. ^{*e*}30 mol % NHTf₂ was used instead of TfOH.

cyanoindole **4q** by utilizing 30 mol % of NHTf₂ instead of TfOH. The investigation of aliphatic substrates showed that linear aldehydes **1r** and **1u**, branched aldehydes **1s** and **1t**, and unsaturated aldehyde **1v** afforded the corresponding nitriles in good yield (4r-v).^{18,19}

This strategy for synthesizing nitriles via transoximation was applied to the large-scale synthesis of the synthetic intermediate 10 of Tarceva (Scheme 2).²⁰ The starting aldehyde 9 was

Scheme 2. One-Gram-Scale Synthesis of the Precursor Nitrile of Tarceva



prepared by dialkylation of aldehyde 7 using 2-bromoethyl methyl ether with K_2CO_3 in DMF at 100 °C for 5 h. The aldehyde 9 (1.5 g) was reacted with oxime 2c at a very mild temperature (~23 °C) to provide the desired nitrile 10 (1.4 g; 94%).

The reaction mechanism was investigated next. *O*-Ms-oxime **3ab** as a starting material was prepared from 2-naphthaldoxime²¹ and then used for nitrile synthesis in the presence of a catalytic Brønsted acid (Scheme 3a). The reaction proceeded well and gave the corresponding nitrile **4a** in 93% yield, thereby Scheme 3. (a) Nitrile Synthesis from O-Ms-oxime 3ab. (b) Investigation of the Isotope Effect in the Conversion of O-Ms-oxime 3ab to Nitrile



confirming that the aldehyde is converted to the corresponding oxime via transoximation and the desired nitrile is generated from the oxime. We observed the appearance of reaction in situ with **1a** and **2b** catalyzed by TfOH using ¹H NMR (Figure 3).



Figure 3. Reaction behavior in situ between 1a and 2b.

Within 8 h, aldehyde 1a was quickly consumed and converted to Ms-oxime 3ab. However, transformation from oxime 3ab to nitrile 4a was very slow, and it took 51 h to complete the reaction after confirming the first generation of nitrile 4a. Therefore, we also investigated the kinetic isotope effect for the deprotonation yielding nitrile 4a from oxime 3ab (Scheme 3b). The result, $k_{\rm H}/k_{\rm D} = 2.5$, indicated that deprotonation of the oxime is the rate-determining step in the transformation from oxime to nitrile.²²

Our findings led us to propose a reaction mechanism for nitrile synthesis via transoximation (Figure 4). Oxime 2 is activated by triflic acid (A) in the presence of trace water to generate NH_2OSO_2Ph with ethyl acetate (B). Then complex B is dehydro-condensed with aldehyde 1 to provide aldoxime C and water. The complex C is converted to nitrile 4, accompanied by the generation of benzenesulfonic acid. Brønsted acid-base reaction with oxime 2 regenerates protonated oxime A and generates aldoxime 3; the reprotonation of 3 by triflic acid or benzenesulfonic acid provides the corresponding nitrile. Water generated from the dehydration condensation (B to C) is consumed during the hydrolysis process (A to B).

In conclusion, we synthesized nitriles from aldehydes via transoximation catalyzed by TfOH under very mild conditions, enabling the use of *O*-protected oxime in place of *O*-protected hydroxylamine as an electron-withdrawing group. The reaction conditions were tolerated by several aromatic/aliphatic aldehydes and gave the desired nitriles in good yield, and the



Figure 4. Proposed reaction mechanism.

reaction could be conducted on a 1 g scale. We confirmed that the nitrile was generated via an *O*-protected aldoxime produced from the aldehyde and an *O*-protected oxime through transoximation. Analysis of the reaction mechanism suggests that deprotonation of the *O*-protected oxime is the ratedetermining step.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.7b01263.

Experimental details and characterization data (PDF)

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The authors declare no competing financial interest.

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REFERENCES

 (1) (a) Fatiadi, A. J. In Preparation and Synthetic Applications of Cyano Compounds; Patai, S., Rappaport, Z., Eds.; Wiley: New York, 1983.
 (b) Miller, J. S.; Manson, J. L. Acc. Chem. Res. 2001, 34, 563.
 (c) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. J. Med. Chem. 2010, 53, 7902.

(2) (a) Sandmeyer, T. Ber. Dtsch. Chem. Ges. 1884, 17, 1633.
(b) Hodgson, H. H. Chem. Rev. 1947, 40, 251. (c) Kim, D. W.; Song, C. E.; Chi, D. Y. J. Org. Chem. 2003, 68, 4281.

(3) (a) Zhou, W.; Zhang, L.; Jiao, N. Angew. Chem., Int. Ed. 2009, 48, 7094. (b) Shu, Z.; Ye, Y.; Deng, Y.; Zhang, Y.; Wang, J. Angew. Chem.,

Letter

Int. Ed. 2013, 52, 10573. (c) Liu, J.; Zheng, H.-X.; Yao, C.-Z.; Sun, B.-F.; Kang, Y.-B. J. Am. Chem. Soc. 2016, 138, 3294–3297.

(4) Selected examples: (a) Oishi, T.; Yamaguchi, K.; Mizuno, N. Angew. Chem., Int. Ed. 2009, 48, 6286. (b) Shimojo, H.; Moriyama, K.; Togo, H. Synthesis 2013, 45, 2155. (c) Yin, W.; Wang, C.; Huang, Y. Org. Lett. 2013, 15, 1850.

(Š) Recent selected examples: (a) Ishihara, K.; Furuya, Y.; Yamamoto, H. Angew. Chem., Int. Ed. 2002, 41, 2983. (b) Yamaguchi, K.; Fujiwara, H.; Ogasawara, Y.; Kotani, M.; Mizuno, N. Angew. Chem., Int. Ed. 2007, 46, 3922. (c) Yu, L.; Li, H.; Zhang, X.; Ye, J.; Liu, J.; Xu, Q.; Lautens, M. Org. Lett. 2014, 16, 1346.

(6) (a) Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M. Org. Lett. 2009, 11, 2461. (b) Sueoka, S.; Mitsudome, T.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. Chem. Commun. 2009, 46, 8243.

(7) Hyodo, K.; Kitagawa, S.; Yamazaki, M.; Uchida, K. *Chem. - Asian J.* **2016**, *11*, 1348.

(8) (a) Rokade, B. V.; Prabhu, K. R. J. Org. Chem. 2012, 77, 5364.
(b) Motiwala, H. F.; Yin, Q.; Aubé, J. Molecules 2016, 21, 45.

(9) (a) Saednya, A. Synthesis 1982, 1982, 190. (b) Enthaler, S.;
Weidauer, M.; Schröder, F. Tetrahedron Lett. 2012, 53, 882.
(c) Zhuang, Y.-J.; Liu, J.; Kang, Y.-B. Tetrahedron Lett. 2016, 57, 5700.
(10) (a) Bellamy, F.; Martz, P.; Streith, J. Tetrahedron Lett. 1974, 15,

(a) Dollar, J. J. J. Loudon, M. J. Org. Chem. 1975, 40, 126.
(c) Laulhe, S.; Gori, S.; Nantz, M. H. J. Org. Chem. 2012, 77, 9334.
(d) Quinn, D. J.; Haun, G. J.; Moura-Letts, G. Tetrahedron Lett. 2016,

57, 3844.
(11) (a) Lai, G.; Bhamare, N. K.; Anderson, W. K. Synlett 2001, 2, 230. (b) Erman, M. B.; Snow, J. W.; Williams, M. J. Tetrahedron Lett.
2000, 41, 6749. (c) Dornan, L. M.; Cao, Q.; Flanagan, J. C. A.;

Crawford, J. J.; Cook, M. J.; Muldoon, M. J. Chem. Commun. 2013, 49, 6030. For other example of nitrogen sources, see: (e) Kelly, C. B.; Lambert, K. M.; Mercadante, M. A.; Ovian, J. M.; Bailey, W. F.; Leadbeater, N. E. Angew. Chem., Int. Ed. 2015, 54, 4241.

(12) Yu et al. have achieved Brønsted acid catalyzed nitrile synthesis for aliphatic aldehydes at ambient temperature; see: An, X. D.; Yu, S. *Org. Lett.* **2015**, *17*, 5064.

(13) (a) Yamafuji, K. *Nature* **1953**, 171, 745. (b) Yamafuji, K.; Omura, H.; Yoshihara, F.; Yoshitake, M.; Oyama, N. *Enzymol.* **1958**, 19, 180.

(14) Hyodo, K.; Togashi, K.; Oishi, N.; Hasegawa, G.; Uchida, K. *Green Chem.* **2016**, *18*, 5788.

(15) MSH reagent (O-(mesitylsulfonyl)hydroxylamine): (a) Johnson,
C. R.; Kirchhoff, R. A.; Corkins, H. G. J. Org. Chem. 1974, 39, 2458.
(b) Grayson, E. J.; Bernardes, G. J. L.; Chalker, J. M.; Boutureira, O.;
Koeppe, J. R.; Davis, B. G. Angew. Chem., Int. Ed. 2011, 50, 4127.
HOSA (hydroxylamine O-sulfonic acid): (c) Brossi, A.; Minamikawa,
J. Org. Synth. 1978, 58, 32.

(16) O-(Diphenylphosphinyl)hydroxylamine (DPPH) and O-(2,4dinitrophenyl)hydroxylamine known as alternatives of MSH were used instead of oxime 2c; however, nitrile 4a was not obtained at all, and only corresponding oximes were observed.

(17) Selected examples: (a) Ramesh, C.; Banerjee, J.; Pal, R.; Das, B. *Adv. Synth. Catal.* **2003**, 345, 557. (b) Varghese, A.; Nizam, A.; Kulkarni, R.; George, L. *Eur. J. Chem.* **2012**, *3*, 247.

(18) Wang, X.; Liu, R.; Jin, Y.; Liang, X. Chem. - Eur. J. 2008, 14, 2679.

(19) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. J. Org. Chem. **1997**, *62*, 6974.

(20) Chandrasekara Reddy, G.; Chandregowda, V.; Venkateswara Rao, G. *Heterocycles* **2007**, *71*, 39.

(21) We also attempted to synthesize oxime 3ac; however, it decomposed immediately.

(22) In the case using oxime 2c, nitrile 4a was smoothly formed compared to using 2b, and the isotope effect was also shown, $k_{\rm H}/k_{\rm D}$ = 2.5; see Figures S4 and S8.