Organic LETTERS

Letter

pubs.acs.org/OrgLett

Tetra-*n*-butylammonium Iodide Catalyzed C−H Azidation of Aldehydes with Thermally Stable Azidobenziodoxolone

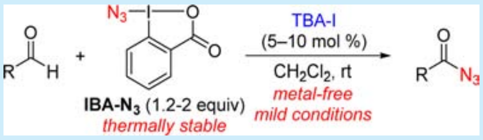
Yukino Shinomoto,[†] Akira Yoshimura,[‡] Hisato Shimizu,[†] Mutsumi Yamazaki,[†] Viktor V. Zhdankin,[‡] and Akio Saito*,[†]

[†]Division of Applied Chemistry, Institute of Engineering, Tokyo University of Agriculture and Technology, 2-24-16 Naka-cho, Koganei, Tokyo 184-8588, Japan

[‡]Department of Chemistry and Biochemistry, University of Minnesota Duluth, Duluth, Minnesota 55812, United States

Supporting Information

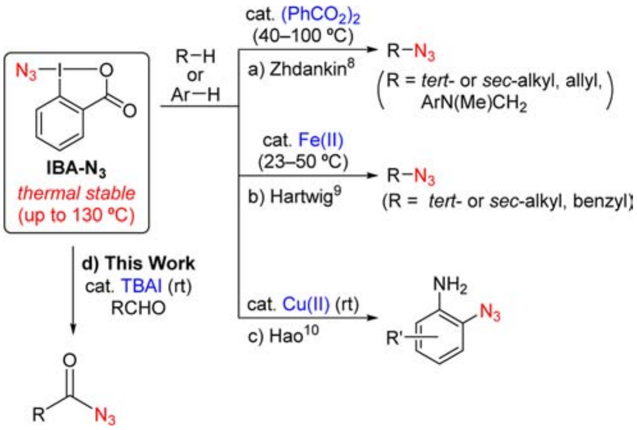
ABSTRACT: Tetra-*n*-butylammonium iodide can efficiently catalyze direct azidation of aldehyde C−H bonds with thermally stable azidobenziodoxolone at room temperature. Compared to conventional methods, which require excessive amounts of highly explosive azide sources, this is a safe and convenient procedure.



Acyl azides are useful and versatile precursors for conversion reactions to isocyanates, amides, heterocycles, and other important products.[1] These reactions have been applied to the synthesis of biologically active substances[2] and functional polymers.[3] Although acyl azides are commonly prepared from acyl chlorides or mixed anhydrides and NaN$_3$,[1] such a traditional method not only requires the additional step of leaving group introduction but also wastes these leaving groups. On the other hand, the direct azidation of aldehyde C−H bonds provides a more efficient and atom-economical procedure for the synthesis of acyl azides. IN$_3$ has been known to be an effective reagent for the C−H azidation of aldehydes, which proceeds via a radical mechanism.[4] Furthermore, these reactions can be achieved by combinations of various oxidants with TMSN$_3$ or azide salts,[5,6] and modified methods using these reagent systems bring about the formation of carbamoyl azides via the Curtius rearrangement of acyl azides.[4,7] However, in all cases, the highly hazardous azide sources are required in excessive amounts (2−5 equiv).

Zhdankin et al. have reported that azidobenziodoxolone (IBA−N$_3$), which is thermally stable (up to 130 °C) and can be stored for a long time, worked well for the C−H azidation of various organic substrates (Scheme 1a).[8] Although the thermal stability of IBA−N$_3$ allows its use at higher temperature, all of the reactions proceed under thermal conditions (up to 100 °C) in the presence of a radical initiator (benzoyl peroxide). Very recently, Hartwig et al. have reported that C−H azidation of simple alkanes and benzyl compounds with IBA−N$_3$ can be catalyzed by Fe(II) under mild conditions (23−50 °C, Scheme 1b).[9] Hao et al. have developed Cu(II)-catalyzed azidation of *o*-C−H bonds of anilines with IBA−N$_3$ at room temperature (Scheme 1c).[10] However, there are only a few reports on the use of IBA−N$_3$ in organic syntheses.[11,12] To the best of our knowledge, non-metal-catalyzed C−H azidation with IBA−N$_3$ under mild conditions is still unknown. Herein, we report the metal-free and mild C−H azidation of aldehydes with IBA−N$_3$ (Scheme 1d).

Scheme 1. C−H Azidation with IBA−N$_3$



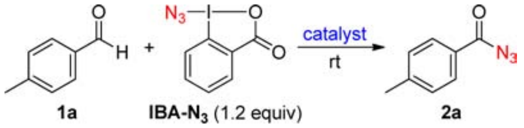
Our initial attempts of non-metal-catalyzed C−H azidation of aldehyde **1a** with IBA−N$_3$ are summarized in Table 1. Since quaternary ammonium salts have been reported as efficient catalysts in oxidative conversions mediated by I(III) reagents[13] and also in radical reactions,[14] we expected that quaternary ammonium salts would work well as activators for reactions of IBA−N$_3$ and/or as radical initiators. Therefore, **1a** was treated with IBA−N$_3$ (1.2 equiv) in the presence of tetra-*n*-butylammonium iodide (TBAI, 20 mol %) in various solvents at room temperature for 4 h (Table 1, entries 1−5). Among tested solvents, CH$_2$Cl$_2$ was the best, and acyl azide **2a** was obtained in 76% yield (entry 1). To our delight, when the catalytic amount of TBAI was decreased to 10 mol %, the yield of **2a** was improved up to 82% at room temperature for 6 h (entry 7). The reaction in the presence of 10 mol % tetraethylammonium iodide (TEAI) also showed a good result, although with detection of a trace amount of **1a** (entry 9). On

Received: September 3, 2015
Published: October 22, 2015

© 2015 American Chemical Society

DOI: 10.1021/acs.orglett.5b02543
Org. Lett. 2015, 17, 5212−5215

Table 1. Optimization of the C−H Azidation of 1a



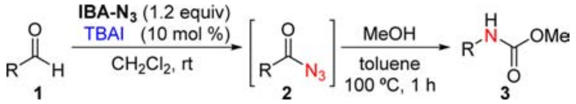
entry	catalyst (mol %)	solvent	time (h)	yield (%) of **2a**[a]	recov (%) of **1a**[a]
1	TBAI (20)	CH_2Cl_2	4	76	4
2	TBAI (20)	$CHCl_3$	4	46	6
3	TBAI (20)	MeCN	4	63	13
4	TBAI (20)	THF	4	trace	85
5	TBAI (20)	MeOH	4	10	61
6	TBAI (10)	CH_2Cl_2	4	76	15
7	TBAI (10)	CH_2Cl_2	6	82	0
8	TBAI (5)	CH_2Cl_2	6	66	0
9	TEAI (10)	CH_2Cl_2	6	81	trace
10	KI (10)	CH_2Cl_2	6	16	0
11	TBABr (10)	CH_2Cl_2	6	22	43
12	TMSCl (10)	CH_2Cl_2	6	trace	trace
13		CH_2Cl_2	4	0	87
14[b]	TBAI (10)	CH_2Cl_2	6	0	quant

[a] The yield was determined by ^1H NMR analysis using toluene as internal standard. [b] TEMPO (2 equiv) was added.

the other hand, the use of KI or trimethylsilyl chloride (TMSCl) as a catalyst afforded a complex mixture including **2a** (entries 10 and 12). The reaction in the presence of TBABr or in the absence of catalyst did not proceed smoothly(entries 11 and 13). It should be mentioned that the TBAI-catalyzed process was hampered by the addition of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) as a radical inhibitor (entry 14 vs 7), which is indicative of a radical mechanism of this reaction.

At the next step, the azidation of various aldehydes under optimized reaction conditions was investigated (Table 2). Since some acyl azides **2** were partially hydrolyzed during the purification by silica gel column chromatography, products **2** were converted to carbamates **3** by the Curtius rearrangement in the presence of MeOH in toluene at 100 °C. Thus, after the Curtius rearrangement of product **2a**, carbamate **3a** was isolated in 66% yield (Table 2, entry 1). Similar to **1a**, aromatic aldehydes **1b−e** reacted with IBA−N_3 in the presence of TBAI at room temperature to give **3b−e** in 58−87% after the Curtius rearrangement (entries 2−5). Although halogen-substituted **1f** and **1g** required 2 equiv of IBA−N_3, the corresponding products **3f** and **3g** were obtained in 74% and 59% yields, respectively (entries 6 and 7). In the case of nitro-substituted **1h**, addition of I_2 along with TBAI brought about superior results (entry 8 vs 9).[15] The TBAI/I_2/IBA−N_3 system could be applied to the reaction of the electron-deficient heteroaromatic aldehyde **1i** (entry 10). On the other hand, the use of 5 mol % of TBAI in the TBAI/IBA−N_3 system was effective for the electron-rich heteroaromatic aldehyde **1j** (entry 11) and aliphatic aldehydes **1k−m** (entries 12−14). Unfortunately, in the cases of alkenyl aldehydes such as cinnamaldehyde and 2-allylbenzaldehyde, considerable amounts of starting materials were recovered.

Table 2. Scope of Aldehydes 1 by TBAI/IBA−N_3 Systems

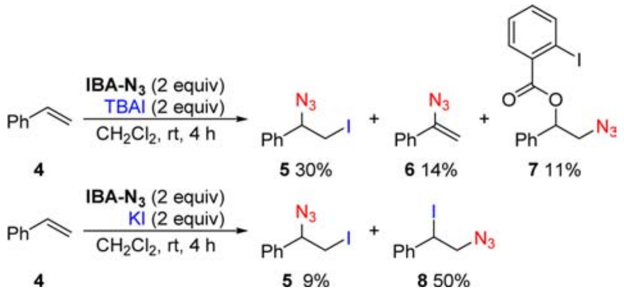


entry	1	R	time (h)	yield (%) of **2**[a]	yield (%) of **3**[b]
1	**1a**	*p*-MeC_6H_4	6	82	66
2	**1b**	*p*-MeOC_6H_4	6	79	58
3	**1c**	Ph	8	nd[c]	62
4	**1d**	1-naphthyl	4	nd[c]	62
5	**1e**	2-naphthyl	24	88	87
6[d]	**1f**	*p*-BrC_6H_4	8	72	74
7[d]	**1g**	*p*-FC_6H_4	6	nd[c]	59
8	**1h**	*p*-$NO_2C_6H_4$	24	nd[c]	4
9[d,e]	**1h**	*p*-$NO_2C_6H_4$	24	nd[c]	34
10[d,e]	**1i**	2-pyridinyl	24	66	53
11[f]	**1j**	2-thienyl	6	51	41
12[f]	**1k**	Cy	6	nd[c]	42
13[f]	**1l**	$CH_3(CH_2)_{10}$	6	nd[c]	56
14[f]	**1m**	$Ph(CH_2)_2$	6	51	52

[a] The yield was determined by ^1H NMR analysis using toluene as internal standard. [b] Isolated yields. [c] Yields were not determined. [d] IBA−N_3: 2 equiv. [e] 10 mol % I_2 was added along with TBAI. [f] TBAI: 5 mol %.

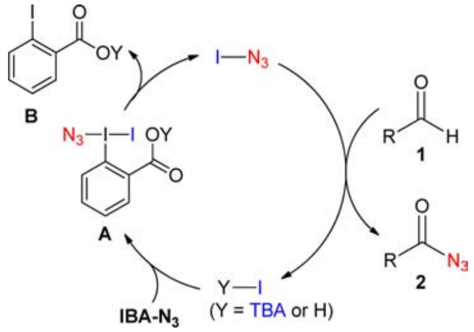
The iodoazidations of alkenes with NaN_3 and iodide salts in the presence of oxidants (such as CAN, Oxone, $NaIO_4$) have been reported to produce anti-Markovnikov adducts via a radical mechanism.[16] However, the TBAI/IBA−N_3 system afforded Markovnikov adduct **5** and alkenyl azide **6**, which is produced from **5** by *β*-elimination of HI, as main products (Scheme 2). These results suggest the generation of IN_3 in the TBAI/IBA−N_3 systems. It is known that the IN_3-mediated iodoazidation of alkenes proceeds via Markovnikov addition by an ionic mechanism, in contrast with a radical mechanism in the C−H azidation of aldehydes.[4,17] On the other hand, the iodoazidation of **4** using KI/IBA−N_3 system preferably proceed via anti-Markovnikov addition (Scheme 2), which might be indicative of the generation of azido radical prior to that of IN_3.[16c] Although the details of effect of countercation still remains unclear, the inefficiency of KI catalyst in the C−H azidation of aldehydes would be due to such a different mechanism.

Scheme 2. Iodoazidation of 4 with TBAI/IBA−N_3 or KI/IBA−N_3 System



On the basis of these results and previous reports on IN_3-mediated C−H azidation of aldehydes,[4] a plausible catalytic cycle for the present C−H azidation is illustrated in Scheme 3. That is, IN_3 would be generated via a formal reductive elimination of aryl iodide **B** from 10-I-3 intermediate **A**, which would be formed by IBA−N_3 and TBAI (or the generated HI). The formation of the similar 10-I-3 intermediate was observed in the mixture of trifluoromethylbenziodoxolone (Togni reagent) and TBAI.[13e] From the catalytically generated IN_3, iodine radical ($I^\bullet$) is released, and then H-abstraction of

Scheme 3. Plausible Catalytic Cycle



aldehydes by I$^\bullet$ brings about the regeneration of HI along with the formation of acyl radical, which leads to acyl azides by the coupling with azido radical.

In summary, we have developed a metal-free and mild procedure for the C−H azidation of aldehydes with IBA−N$_3$ in the presence of TBAI catalyst, which is required for the catalytic generation of IN$_3$. Compared to conventional methods with excessive amounts of highly explosive azide sources, the present procedure is safer. Further studies on metal-free and mild C−H azidation of other substrates with IBA−N$_3$ are underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02543.

Experimental procedures and physical data for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: akio-sai@cc.tuat.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partially supported by JSPS Grants-in-Aid for Young Scientists (B) (Grant No. 24790024) and Scientific Research (C) (Grant No. 15K07852) and by the Asahi Glass Foundation. V.V.Z. is also thankful to the National Science Foundation (CHE-1262479).

■ REFERENCES

(1) For reviews, see: (a) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188. (b) Bräse, S., Banert, K., Eds. *Organic Azides: Syntheses and Applications*; Wiley−VCH: Weinheim, 2010.

(2) Recent examples: (a) LaMarche, M. J.; Leeds, J. A.; Dzink-Fox, J.; Gunderson, K.; Krastel, P.; Memmert, K.; Patane, M. A.; Rann, E. M.; Schmitt, E.; Tiamfook, S.; Wang, B. *J. Med. Chem.* **2011**, *54*, 2517. (b) Zhao, L.; Zhang, Y.; Dai, C.; Guzi, T.; Wiswell, D.; Seghezzi, W.; Parry, D.; Fischmann, T.; Siddiqui, M. A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7216. (c) Mhidia, R.; Boll, E.; Fécourt, F.; Ermolenko, M.; Ollivier, N.; Sasaki, K.; Crich, D.; Delpech, B.; Melnyk, O. *Bioorg. Med. Chem.* **2013**, *21*, 3479. (d) Scola, P. M.; Sun, L.-Q.; Wang, A. X.; Chen, J.; Sin, N.; Venables, B. L.; Sit, S.-Y.; Chen, Y.; Cocuzza, A.; Bilder, D. M.; D'Andrea, S. V.; Zheng, B.; Hewawasam, P.; Tu, Y.; Friborg, J.; Falk, P.; Hernandez, D.; Levine, S.; Chen, C.; Yu, F.; Sheaffer, A. K.; Zhai, G.; Barry, D.; Knipe, J. O.; Han, Y.-H.; Schartman, R.; Donoso, M.; Mosure, K.; Sinz, M. W.; Zvyaga, T.; Good, A. C.; Rajamani, R.; Kish, K.; Tredup, J.; Klei, H. E.; Gao, Q.; Mueller, L.; Colonno, R. J.; Grasela, D. M.; Adams, S. P.; Loy, J.; Levesque, P. C.; Sun, H.; Shi, H.; Sun, L.; Warner, W.; Li, D.; Zhu, J.; Meanwell, N. A.; McPhee, F. *J. Med. Chem.* **2014**, *57*, 1730.

(3) Recent examples: (a) Sagi, A.; Weinstain, R.; Karton, N.; Shabat, D. *J. Am. Chem. Soc.* **2008**, *130*, 5434. (b) Zenner, M. D.; Xia, Y.; Chen, J. S.; Kessler, M. K. *ChemSusChem* **2013**, *6*, 1182. (c) Ikeda, T.; Oikawa, D.; Shimasaki, T.; Teramoto, N.; Shibata, M. *Polymer* **2013**, *54*, 3206. (d) Kroon, R.; Diaz de Zerio Mendaza, A.; Himmelberger, S.; Bergqvist, J.; Bäcke, O.; Faria, G. C.; Gao, F.; Obaid, A.; Zhuang, W.; Gedefaw, D.; Olsson, E.; Inganäs, O.; Salleo, A.; Müller, C.; Andersson, M. R. *J. Am. Chem. Soc.* **2014**, *136*, 11578.

(4) Marinescu, L.; Thinggaard, J.; Thomsen, I. B.; Bols, M. *J. Org. Chem.* **2003**, *68*, 9453.

(5) (a) CrO$_3$/TMAN$_3$: Lee, J. G.; Kwak, K. H. *Tetrahedron Lett.* **1992**, *33*, 3165. (b) PCC/NaN$_3$: Reddy, P. S.; Yadgiri, P.; Lumin, S.; Falck, J. R. *Synth. Commun.* **1988**, *18*, 545. (c) MnO$_2$/SiCl$_4$/NaN$_3$: Elmorsy, S. S. *Tetrahedron Lett.* **1995**, *36*, 1341.

(6) (a) PhI(OAc)$_2$/NaN$_3$: Chen, D. J.; Chen, Z. C. *Tetrahedron Lett.* **2000**, *41*, 7361. (b) DMP/NaN$_3$: Bose, D. S.; Reddy, A. V. N. *Tetrahedron Lett.* **2003**, *44*, 3543. (c) ^{t}BuOCl/NaN$_3$: Arote, N. D.; Akamanchi, K. G. *Tetrahedron Lett.* **2007**, *48*, 5661. (d) NHC catalyst/3,3′,5,5′-tetra-*tert*-butyldiphenoquinone/TMSN$_3$: De Sarkar, S.; Studer, A. *Org. Lett.* **2010**, *12*, 1992.

(7) (a) Pedersen, C. M.; Marinescu, L. G.; Bols, M. *Org. Biomol. Chem.* **2005**, *3*, 816. (b) Marinescu, L. G.; Pedersen, M. C.; Bols, M. *Tetrahedron* **2005**, *61*, 123. (c) Brandt, J. C.; Wirth, T. *Beilstein J. Org. Chem.* **2009**, DOI: 10.3762/bjoc.5.30.

(8) (a) Zhdankin, V. V.; Krasutsky, A. P.; Kuehl, C. J.; Simonsen, A. J.; Woodward, J. K.; Mismash, B.; Bolz, J. T. *J. Am. Chem. Soc.* **1996**, *118*, 5192. (b) Krasutsky, A. P.; Kuehl, C. J.; Zhdankin, V. V. *Synlett* **1995**, *1995*, 1081. (c) Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Fromaneck, M. S.; Bolz, J. T. *Tetrahedron Lett.* **1994**, *35*, 9677. (d) Modified procedure for the preparation of IBA−N$_3$: Kita, Y.; Akai, S.; Okuno, T.; Takada, T.; Tohma, H. *Heterocycles* **1996**, *42*, 47.

(9) (a) Sharma, A.; Hartwig, J. F. *Nature* **2015**, *517*, 600. See also highlights of this paper: (b) Vita, M. V.; Waser, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 5290.

(10) Fan, Y.; Wan, W.; Ma, G.; Gao, W.; Jiang, H.; Zhu, S.; Hao, J. *Chem. Commun.* **2014**, *50*, 5733.

(11) Addition to alkenes with IBA−N$_3$: (a) Zhang, B.; Studer, A. *Org. Lett.* **2013**, *15*, 4548. (b) Kong, W.; Merino, E.; Nevado, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 5078. (c) Yin, H.; Wang, T.; Jiao, N. *Org. Lett.* **2014**, *16*, 2302. (d) Zhu, L.; Yu, H.; Xu, Z.; Jiang, X.; Lin, L.; Wang, R. *Org. Lett.* **2014**, *16*, 1562.

(12) Examples of other azidobenziodoxoles: (a) Zn(II) catalysis: Vita, M. V.; Waser, J. *Org. Lett.* **2013**, *15*, 3246. (b) Fe(II) catalysis: Deng, Q.-H.; Bleith, T.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2013**, *135*, 5356.

(13) (a) Tohma, H.; Takizawa, S.; Watanabe, H.; Kita, Y. *Tetrahedron Lett.* **1998**, *39*, 4547. (b) Ye, Y.; Zheng, C.; Fan, R. *Org. Lett.* **2009**, *11*, 3156. (c) Eisenberger, P.; Gischig, S.; Togni, A. *Chem. - Eur. J.* **2006**, *12*, 2579. (d) Zhang, B.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Studer, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 10792. (e) Kong, W.; Casimiro, M.; Fuentes, N.; Merino, E.; Nevado, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 13086. Recent reviews: (f) Merritt, E. A.; Olofsson, B. *Synthesis* **2011**, *2011*, 517. (g) Zhdankin, V. V. *Hypervalent Iodine Chemistry: Preparation, Structure and Synthetic Application of Polyvalent Iodine Compounds*; Wiley: Chichester, 2013.

(14) Recent reviews: (a) Finkbeiner, P.; Nachtsheim, B. F. *Synthesis* **2013**, *45*, 979. (b) Wu, X.-F.; Gong, J.-L.; Qi, X. *Org. Biomol. Chem.* **2014**, *12*, 5807.

(15) In this case, TBAI$_3$ might be involved rather than IN$_3$. It is known that ammonium triiodide (TBAI$_3$) is in equilibrium with I$_2$ and TBAI and triiodide (I$_3^-$) is excited by visible light (ambient laboratory light) to generate an iodine radical (I$^\bullet$) and an iodine radical anion (I$_2^{\bullet-}$). See: (a) Gardner, J. M.; Abrahamsson, M.;

Farnum, B. H.; Meyer, G. J. *J. Am. Chem. Soc.* **2009**, *131*, 16206. (b) Boschloo, G.; Hagfeldt, A. *Acc. Chem. Res.* **2009**, *42*, 1819. (c) Kiyokawa, K.; Kosaka, T.; Minakata, S. *Org. Lett.* **2013**, *15*, 4858.

(16) (a) Nair, V.; George, T. G.; Sheeba, V.; Augustine, A.; Balagopal, L.; Nair, L. G. *Synlett* **2000**, 1597. (b) Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Tetrahedron Lett.* **2002**, *43*, 1201. (c) Chouthaiwale, P. V.; Karabal, P. U.; Suryavanshi, G.; Sudalai, A. *Synthesis* **2010**, *2010*, 3879.

(17) (a) Hassner, A.; Levy, L. *J. Am. Chem. Soc.* **1965**, *87*, 4203. (b) Hassner, A. *Acc. Chem. Res.* **1971**, *4*, 9. (c) Wang, Y.-F.; Lonca, G. H.; Le Runigo, M.; Chiba, S. *Org. Lett.* **2014**, *16*, 4272.

DOI: 10.1021/acs.orglett.5b02543