CONTRIBUTION FOR:

ELECTRONIC ENCYCLOPEDIA OF REAGENTS FOR ORGANIC SYNTHESIS

1-AZIDO-3,3-DIMETHYL-3-(1H)-1,2-BENZIODOXOLONE

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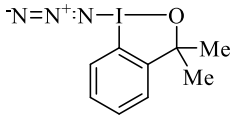
Reagents Details



$C_9H_{10}IN_3O$ 1-Azido-3,3-Dimethyl-3-(1H)-1,2-BenziodoXolone (ADBX) (MW 303.102)

(reagent used as azide source)

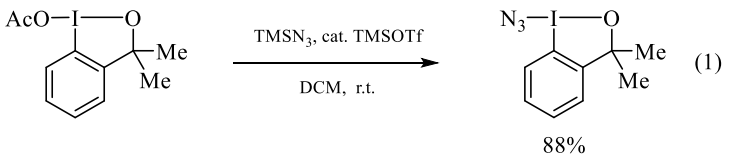
Physical Data: mp (Dec.) 112-117 °C.

Solubility: very soluble (>10 mg/mL) in DMSO, DMF, THF, CAN, DCM, DCE, EtOAc, Acetone; soluble (~10mg/mL) in Toluene, Xylene; partially soluble (<10 gm/mL) in EtOH, MeOH, Et_2O; not soluble in Pentane, Hexane, Water.

Form Supplied in: yellow crystals; not available commercially.

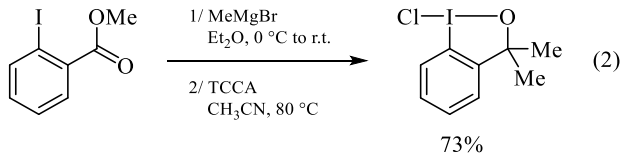
Analysis of Reagent Purity: purity is analyzed by ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 1 H; Ar*H*), 7.55 (m, 2 H; Ar*H*), 7.23 (d, *J* = 7.2 Hz, 1 H; Ar*H*), 1.53 (s, 6 H; $(CH_3)_2$) and ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.2, 130.9, 130.4, 127.8, 126.8, 114.0, 83.2, 29.6.

First Preparative Method:[1,2] The first synthesis of ADBX was reported in 1996 by Kita and co-workers by simple azidation of non-commercially available 1-acetoxy-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole with trimethylsilyl azide in presence of trimethylsilyl triflate (eq. 1).[1]



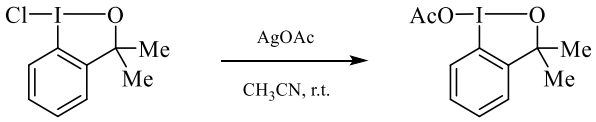
In 2017, Waser and co-workers reported an optimized synthesis starting from commercially available methyl 2-iodobenzoate (eq. 2-4).[2] The ester is first methylated twice with methyl

magnesium bromide, followed by an oxidation in presence of 1,3,5-trichloro-1,3,5-triazinane-2,4,6-trione (trichloroisocyanuric acid, TCCA) to afford 1-chloro-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole in 73% yield (eq. 2). The chlorine is then substituted by treatment with silver acetate in acetonitrile to obtain 1-acetoxy-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole in 93% yield (eq. 3). The acetate is activated by treatment with freshly distilled trimethylsilyl triflate and reacted with trimethylsilylazide to afford ADBX in 96% yield (eq. 4). Better reproducibility was obtained by starting the reaction at 0 °C instead of room temperature. It is recommended to prepare only moderate quantities of the compound (up to 2 g) and store it in a refrigerator because it is subject to exothermic decomposition. Due to the potential exothermic decomposition associated with all high energy hypervalent iodine compounds, all the steps have to be conducted behind a safety shield.



(2)

73%



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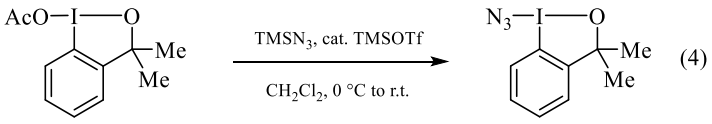
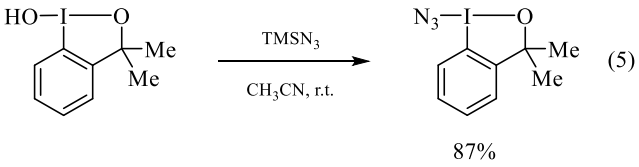
93%



(4)

96%

Second Preparative Method:[3] As reported in 1996 by Zhdankin and co-workers, ADBX can also be obtained from 1-hydroxy-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole stirred at room temperature in dry acetonitrile in presence of trimethylsilylazide for 10 to 15 hours in 87% yield (eq. 5).[3] The required hydroxybenziodoxole can be accessed in three steps from commercially available methyl 2-iodobenzoate in 22% overall yield.[4]



(5)

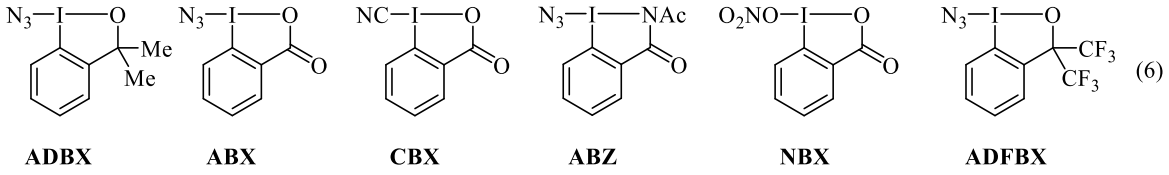
Purification: ADBX can be purified by a simple trituration with *n*-hexane at room temperature.

Handling, Storage and Precautions: the reagent is stable to air at room temperature. Prolonged exposure to light and higher temperature may cause decomposition (**CAUTION**: an exothermic degradation was observed by DSC at 107-156 °C (843 J/g, peak maximum at 10 mV), however the degradation observed is less rapid than the corresponding 1-azido-1,2-benziodoxol-3(1H)-one (Zhdankin's reagent, ABX, 115-131 °C, 1047 J/g, peak maximum at 132 mV). For long time storage ADBX should be protected from light in a refrigerator under inert atmosphere. Its specific toxicity has not been reported up to date.

Introduction

1-Azido-3,3-dimethyl-3-(1H)-1,2-benziodoxolone, called thereafter ADBX, was reported for the first time in 1996 in parallel by Kita and co-workers in April,[1] and by Zhdankin *et al.* in June,[3] two years after the first reported synthesis of 1-azido-1,2-benziodoxol-3(1H)-one (ABX, https://doi.org/10.1002/047084289X.rn02053 on EROS) by Zhdankin and co-workers (eq. 6).[5] In their work, Kita and co-workers presented a full characterization of ADBX, as well as the synthesis of other benziodoxole reagents, such as ABX, Cyanobenziodoxolone (CBX), Azidobenziodazolone (ABZ), and Nitratobenziodoxolone (NBX). Zhdankin and co-workers focused more on ADBX and ABX, but they also presented the synthesis of azidoditrifluoromethylbenziodoxole (ADFBX). Moreover, they reported the first application of these reagents for azidation reactions as described in the following section. The following two decades of research have demonstrated that ABX (and its safer tosyl ABZ analogue)[6] were

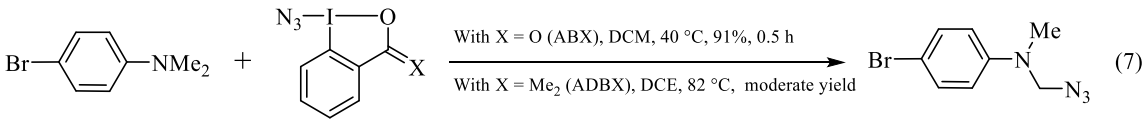
superior reagents for azidation reactions involving radical intermediates or transition metal catalysts, whereas ADBX is more suited for electrophilic azidation in presence of Lewis acids.



(6)

First azidation of organic substrates

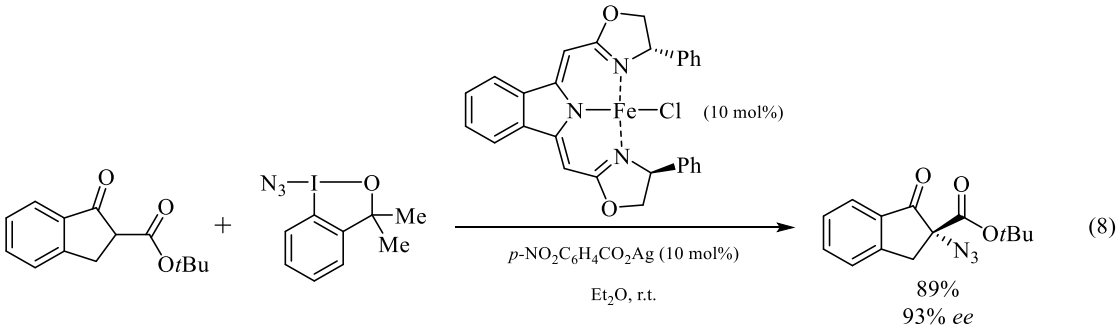
Azidation using ADBX was first applied to radical-based transformations assuming a reactivity similar to the one of non-cyclic azido hypervalent iodine reagents generated in situ from iodosylbenzene and trimethylsilyl azide as previously reported by Magnus and co-workers.[7] Zhdankin and co-workers reported the formation of *N*-azidomethyl-*N*-methylanilines in moderate yield starting from *N*,*N*-dimethylanilines using ADBX in dichloroethane at reflux (eq. 7).[3] In comparison, high yield of azidation was obtained with ABX already at 40 °C. From these studies, it was concluded that ADBX is less suited for radical-based processes.

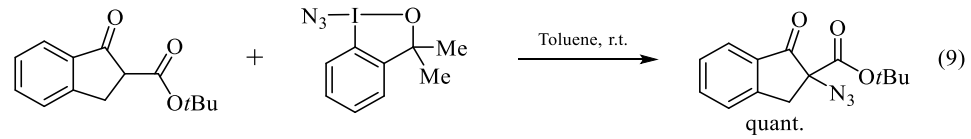


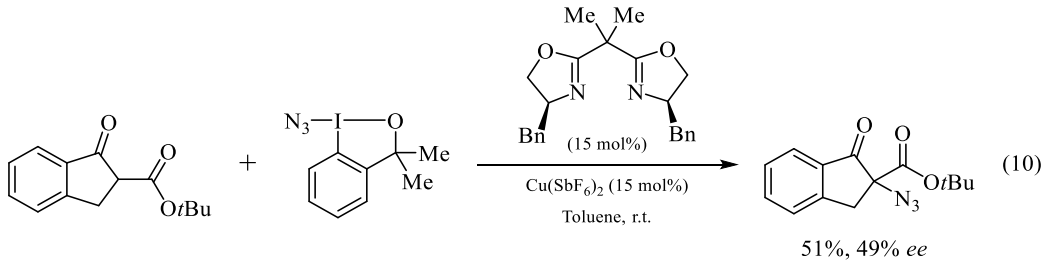
(7)

Azidation of *β*-Keto Esters

In 2013, the azidation of *β*-keto esters was accomplished using ADBX as electrophilic reagent in parallel by Gade and co-workers[8] and Waser and co-workers (eq. 8-10).[9] Gade and co-workers reported the use of a chiral iron pincer complex to achieve azidation with enantioselectivity up to 93% (eq. 8). The azidation reaction reported by Waser and co-workers proceeded in good to quantitative yields without any additives (eq. 9). Using a copper(II) catalyst with a chiral BOX ligand, 49% of enantiomeric excess could be obtained as a proof of concept for asymmetric induction (eq. 10).

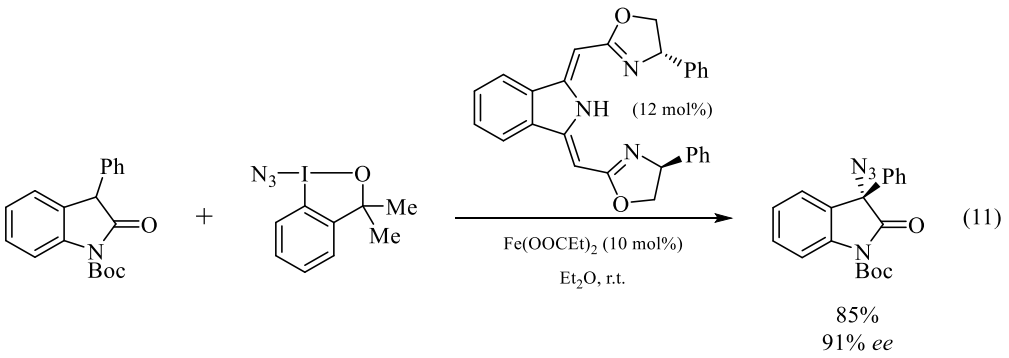






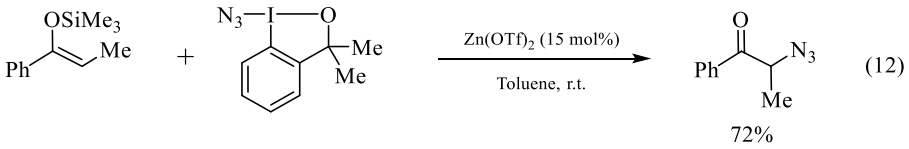
Azidation of Oxindoles

In 2013, Gade and co-workers also reported an oxindole azidation using slightly modified reaction conditions when compared to *β*-keto esters. This reaction was achieved in high yield and enantioselectivity (eq. 11).[8]



Azidation of Silyl Enol Ethers

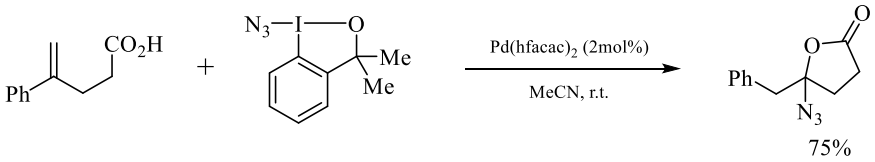
The azidation of silyl enol ethers was also reported by Waser and co-workers together with the azidation of *β*-keto esters (eq. 12).[9] This reaction is also efficiently performed using ADBX. The azidated products are obtained in good to excellent yields with a broad range of substituted silyl enol ethers. The azide can be obtained with both linear and cyclic enol ethers. Two years later, the same group also combined this method with palladium catalyzed enantioselective decarboxylation as a second step to access enantio-enriched homoallylic azides.[10]



(12)

Azidolactonisation of Alkenes

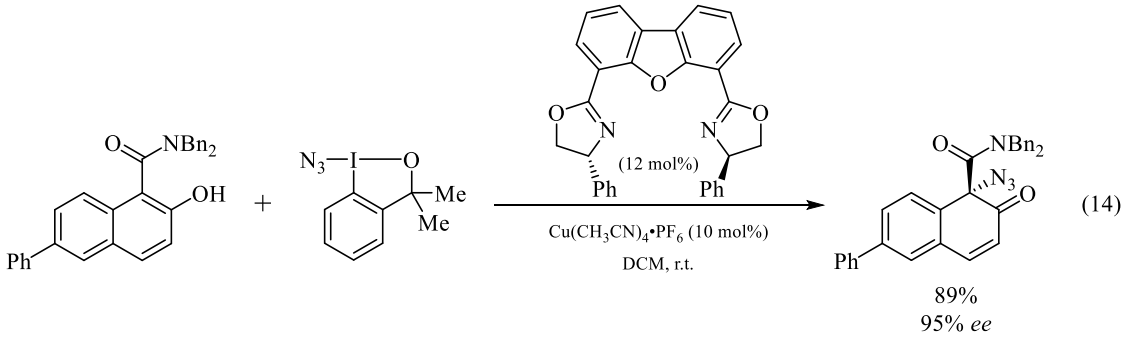
(1,1)-Azidolactones can be directly accessed from alkenes by reaction with ADBX under Pd-catalysis (eq. 13).[2] Lewis acid activation of the hypervalent iodine, followed by reaction with the olefin, lactonization, 1,2-aryl shift and azidation has been proposed to rationalize the formation of the observed product. In case of an alkyl substituent on the olefin, 1,2-azidolactones were obtained in moderate yields.



(13)

Enantioselective Azidation of *β*-Naphtols

Deng and co-workers reported in 2019 an electrophilic dearomative azidation of *β*-naphthols (eq. 14).[11] A copper catalysis with a chiral dbfox ligand led to product formation with up to 90% of enantiomeric excess for esters and 96% ee for amides. Several functional groups were well tolerated under mild reaction conditions.



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