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Unified Strategy for Iodine(III)-Mediated Halogenation and Azidation of 1,3-Dicarbonyl Compounds

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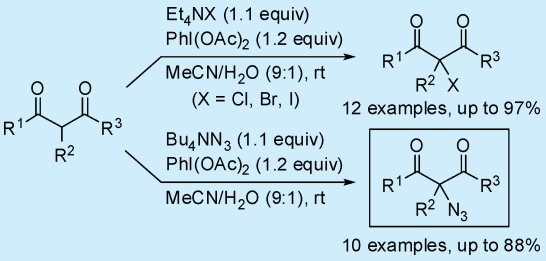
Supporting Information

ABSTRACT: A mild and rapid (diacetoxyiodo)benzene-mediated formal electrophilic α-azidation of 1,3-dicarbonyl compounds using commercially available Bu_4NN_3 as the azide source is reported. The reaction conditions employed are based on optimization studies conducted on the analogous halogenations with Et_4NX (X = Cl, Br, I).



α-Halo and α-azido 1,3-dicarbonyl compounds are fundamentally important synthetic intermediates with wide ranging applications.[1] Often the former is a synthetic precursor to the latter by nucleophilic substitution with NaN_3.[2] Many electrophilic methods exist to access α-halo 1,3-dicarbonyl compounds of which the most used involve the reaction of enolate nucleophiles with electrophilic halogenating agents as sources of X^+.[3] An attractive alternative is the use of in situ generated X^+ equivalents by oxidation or Umpolung of halide salts.[4] Hypervalent iodine(III) reagents[5] in particular have proven to be suitable for such Umpolung strategies.[6,7]

In contrast, direct electrophilic methods to access α-azido 1,3-dicarbonyl compounds are relatively rare. Such methods rely mostly on the use of arylsulfonyl azides as N_3^+ equivalents; however, there is competition between the α-azido and α-diazo products with the former obtained in mostly moderate yields.[8]

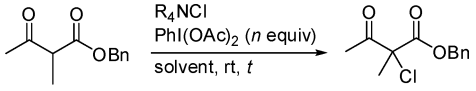
The other sources of N_3^+ are $ArI(N_3)_2$.[9] These reagents are generated in situ from 1 equiv of an aryl-λ^3-iodane and 2 equiv of $TMSN_3$[9,10a] or NaN_3[10b] and consist of an Umpolung of one of the added azide equivalents. However, scope is limited to simple non-α-substituted 1,3-dicarbonyl compounds.

Iodine(III)-mediated formal electrophilic α-azidation of carbonyl compounds has also been reported. In these one-pot procedures, an in situ installed α-leaving group, such as the α-tosyloxy group with Koser's reagent, is substituted by N_3^-.[11] Once again, substrate scope is limited.

The α-azidation of enolizable substrates has very recently attracted much attention. Kirsch reported an iodine(V)-mediated α-azidation method comprising the NaN_3/IBX-SO_3K tandem and substoichiometric amounts of NaI as an additive.[12] Subsequently, Gade[13] and Waser[14] published Lewis acid catalyzed α-azidation procedures utilizing cyclic azido-iodinanes, with the former reporting the first high enantioselectivites with chiral iron(II)-based catalysts. These reports prompted us to disclose our own investigation into the α-azidation of 1,3-dicarbonyls, which was initiated with the goal to develop a system for α-halogenation that could be adopted for α-azidation. The method described herein requires no catalyst, additive, substrate modification, or the synthesis of N_3^+ reagents.[15]

Ammonium salts are mildly acidic and can be easily modified to solubilize counterions in organic solvents. The use of ammonium halides (R_4NX) as sources for X^- in hypervalent iodine-mediated α-halogenation is rare.[16] Thus, and with the above goal in mind, we attempted the α-chlorination of our test substrate **1a** with NH_4Cl as the Cl^- source. Initially, we added 2 equiv of (diacetoxyiodo)benzene (DIB) to an equimolar mixture of **1a** and NH_4Cl in MeCN, which resulted in a heterogeneous reaction mixture that gave the α-chloro product **2a** in 60% conversion after 24 h (Table 1, entry 1).[17] In an

Table 1. Optimization of the DIB-Mediated α-Chlorination[a]



1a **2a**

entry	R_4NCl (equiv)	n	solvent	t	conv[b] (%)
1	H_4NCl (1.1)	2.0	MeCN	24 h	60
2	H_4NCl (1.1)	2.0	MeCN/H_2O (9:1)	24 h	60
3	H_4NCl (1.1) Et_4NCl (0.1)	2.0	MeCN/H_2O (9:1)	6 h	70
4	Et_4NCl (1.1)	2.0	MeCN	1 h	≥98 (90)
5	Et_4NCl (1.1)	2.0	MeCN/H_2O (9:1)	5 min	≥98 (91)
6	Et_4NCl (1.1)	1.2	MeCN/H_2O (9:1)	5 min	≥98 (92)

[a]Reaction conditions: substrate (1.0 mmol), solvent (3 mL). [b]Determined by ^1H NMR spectroscopy of the crude material; yield of isolated product after column chromatography is given in parentheses.

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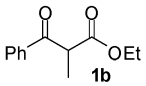
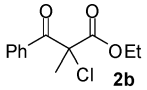
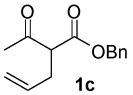
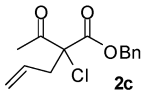
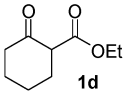
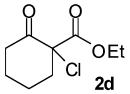
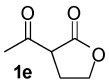
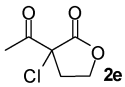
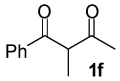
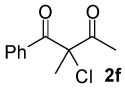
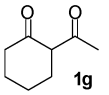
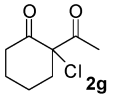
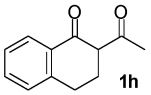
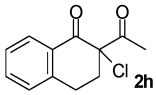
attempt to improve conversion by increasing the solubility of NH_4Cl, we carried out the reaction in $MeCN/H_2O$ (9:1) but observed no improvement (entry 2). A marked acceleration of the reaction was observed when we added 10 mol % of Et_4NCl as phase-transfer catalyst. The reaction mixture became homogeneous with 70% conversion reached after 6 h. This experiment prompted us to examine Et_4NCl as the sole Cl^- source in MeCN. Gratifyingly, this gave a complete conversion to the product in 1 h, with **2a** isolated in 90% yield after chromatography (Table 1, entry 4). Moreover, when using a $MeCN/H_2O$ mixture as the solvent, the reaction time could be shortened to just 5 min (entry 5). Further optimization revealed that 1.2 equiv of DIB was equally effective (entry 6).

With the optimized conditions from Table 1, entry 6, in hand, we examined the substrate scope of this reaction and were pleased to find that β-keto esters **1b** and **1d**, lactone **1e**, as well as 1,3-diketones **1f–h** were α-chlorinated in high yields (Table 2). α-Allyl-substituted substrate **1c** gave poor results in

Table 2. α-Halogenation of 1,3-Dicarbonyl Compounds with the Et_4NX/DIB System (X = Cl, Br, I)[a]

entry	substrate	product	t (min)	yield[b] (%)
1	**1a**	**2a**	5	92
2	 **1b**	 **2b**	360	85
3	 **1c**	 **2c**	2	61[c]
4	 **1d**	 **2d**	5	91
5	 **1e**	 **2e**	5	85
6	 **1f**	 **2f**	50	97
7	 **1g**	 **2g**	5	88
8	 **1h**	 **2h**	3	75
9	**1a**	**2i** (Br)	5	80
10	**1e**	**2j** (Br)	5	72
11	**1g**	**2k** (Br)	5	73
12	**1g**	**2l** (I)	5	72

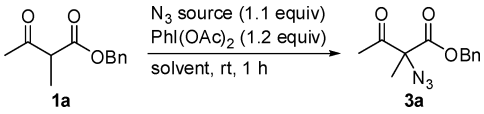
[a]Reaction conditions: substrate (1.0 mmol), Et_4NX (1.1 mmol), DIB (1.2 mmol), $MeCN/H_2O$ (9:1, 3 mL). [b]Isolated yield after column chromatography. [c]MeCN/AcOH (9:1, 3 mL) was used as solvent.

$MeCN/H_2O$. However, carrying out the reaction in MeCN/AcOH (9:1) gave **2c** in an acceptable 61% yield, presumably due to the higher enol content of **1c** in AcOH.

The use of Et_4NX was general with respect to the other halides. Using Et_4NBr as the Br^- source, α-bromination occurred in good yields with substrates **1a**, **1e**, and **1g** (entries 9–11). Similarly, α-iodination of **1g** proceeded within 5 min in 72% yield with Et_4NI as the I^- source.

Having established that the Et_4NX/DIB tandem is an efficient system for α-halogenation, we proceeded to test commercially available Bu_4NN_3 as a N_3^- source for α-azidation. Initial experiments with **1a** under the same conditions for halogenation, that is, adding DIB to a mixture of **1a**/Bu_4NN_3 or adding Bu_4NN_3 to a mixture of **1a**/DIB, were either irreproducible or gave product mixtures.[17,18] However, when combining Bu_4NN_3 and DIB in $MeCN/H_2O$ first, followed by the immediate addition of the substrate in one portion, we were able to detect a rapid consumption of the starting material in a slightly exothermic reaction. To our delight, workup confirmed complete conversion to the α-azido product **3a** which was isolated in 84% yield (Table 3, entry 1). In contrast, all other

Table 3. Optimization of the DIB-Mediated α-Azidation of 1a[a]



1a **3a**

entry	N_3 source	solvent	conv[b] (%)	yield[c] (%)
1	Bu_4NN_3	$MeCN/H_2O$ (9:1)	≥98	84[d]
2	Bu_4NN_3	MeCN	85	70
3	Bu_4NN_3	CH_2Cl_2	82	69
4	Bu_4NN_3	toluene	79	64
5	Bu_4NN_3	Et_2O	74	71
6	Bu_4NN_3	THF	67	46
7	$TMSN_3$	MeCN		
8	NaN_3	$MeCN/H_2O$ (9:1)	trace	

[a]Reaction conditions: substrate (1.0 mmol), solvent (3 mL). [b]Determined by ^1H NMR spectroscopy of the crude material. [c]Isolated yield after column chromatography. [d]Reaction time: 5 min.

solvents tested were inferior to the $MeCN/H_2O$ solvent system (Table 3, entries 2–6), confirming our findings with Et_4NX. Other N_3^- sources were also tested, with no reaction observed with $TMSN_3$ (entry 7)[19] and only traces of **3a** detected with NaN_3 (entry 8).[10b,20] These experiments clearly demonstrate the unique properties of Bu_4NN_3 as a source of N_3^- in our α-azidation reaction.

The α-azidation conditions from Table 3, entry 1, were amenable to a variety of cyclic and acyclic β-keto esters (Table 4, entries 1–9) and a 1,3-diketone (entry 10), with the majority of the corresponding α-azido compounds obtained in fair-to-good yields. Ketones were unreactive under these conditions.

In contrast to α-halo transfer to carbonyl compounds from hypervalent I–X reagents,[6b,21] there is only very limited understanding of α-N_3 transfer to carbonyl compounds from hypervalent I–N_3 reagents. Azidation studies on other substrates have suggested the involvement of azido radicals ($N_3^\bullet$)[19c] or free radical chain mechanisms.[19a,22] In an attempt to probe a radical pathway, we first subjected β-keto ester **1m** with a α-cyclopropyl radical clock to our standard reaction conditions.[23] After 1 h, no α-azido product **3m** was detected with the starting material recovered unchanged, presumably due to steric arguments. Moreover, products **4** and/or **5** originating from a cyclopropylcarbinyl to 3-butenyl radical rearrangement and subsequent hydrogen atom abstraction and/or $N_3^\bullet$ trapping were also not observed (Scheme 1a).[19c,24]

In a second experiment, we conducted the azidation of **1a** in the presence of the radical trap *N-tert*-butyl-α-phenylnitrone (**6**).[19a] This reaction was not significantly inhibited by the

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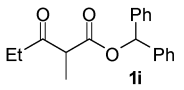
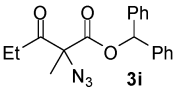
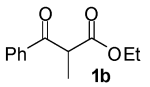
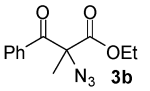
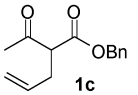
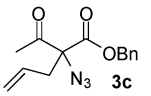
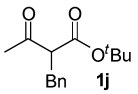
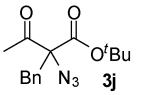
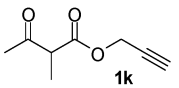
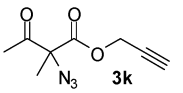
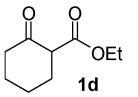
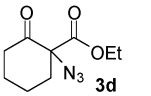
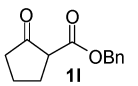
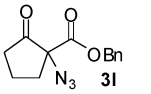
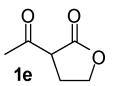
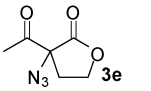
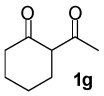
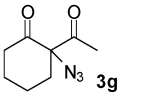
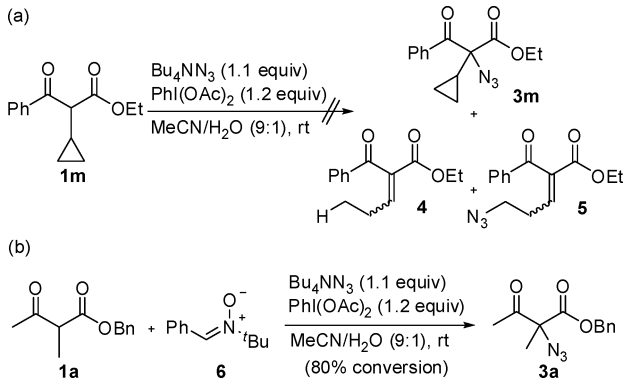
Table 4. α-Azidation of 1,3-Dicarbonyl Compounds with the Bu_4NN_3/DIB System[a]

entry	substrate	product	t (min)	yield[b] (%)
1	**1a**	**3a**	5	84
2	 **1i**	 **3i**	5	83
3	 **1b**	 **3b**	50	40
4	 **1c**	 **3c**	5	77[c]
5	 **1j**	 **3j**	5	61
6	 **1k**	 **3k**	5	67
7	 **1d**	 **3d**	5	74
8	 **1l**	 **3l**	5	53
9	 **1e**	 **3e**	5	88
10	 **1g**	 **3g**	5	79

[a]Reaction conditions: substrate (1.0 equiv), Bu_4NN_3 (1.1 equiv), DIB (1.2 equiv), $MeCN/H_2O$ (9:1, 3 mL). [b]Isolated yield after column chromatography. [c]Bu_4NN_3 (2.1 equiv), DIB (2.1 equiv).

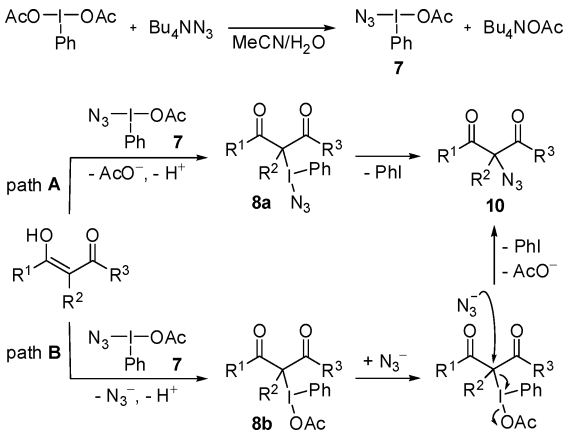
Scheme 1. Probing the Involvement of a Radical Pathway



presence of **6**, with **3a** formed in 80% conversion under our standard reaction conditions (Scheme 1b).

These experiments support an ionic pathway for the α-azidation reaction. On the basis of the stoichiometry used, we propose that the initial mixing of equimolar amounts of Bu_4NN_3 and $PhI(OAc)_2$ generates azidoiodinane **7** (Scheme 2).[25] Such mixed-ligand azido λ^3-iodanes are predicted to be highly reactive due to the unfavorable combination of *trans* influences of the OAc/N_3 ligand set[26] and the absence of a

Scheme 2. Proposed Mechanism for α-Azidation



stabilizing cyclic benziodoxolone structure.[22] Subsequent C–I bond forming attack by the substrate enol tautomer onto **7** can occur by two pathways. The first, resulting from ligand exchange with AcO^-, generates intermediate **8a** which upon reductive elimination of iodobenzene gives the α-azido product **10** (pathway **A**). Alternatively, ligand exchange can occur with the N_3 ligand to give intermediate **8b** (pathway **B**). This can be rationalized by the fact that the I–N bond in **7** is likely to be longer and more polarized than the I–OAc bond.[22,26] Subseqent S_N2 substitution of the hypernucleofuge in **8b** by N_3^- furnishes **10**.[2,27] Support for pathway **B** can also be drawn from the fact that competing formation of the α-OAc product is observed when an excess of AcOH or AcO^- over N_3^- ion is present in the reaction mixture.[18,28]

In conclusion, we have developed a novel, mild and rapid hypervalent iodine-mediated α-azidation of 1,3-dicarbonyl compounds by employing commercially available Bu_4NN_3 as the N_3^- source. The success of this procedure depended on studies conducted with the analogous α-halogenations with Et_4NX that led to crucial choices with respect to solvent and the type of ammonium salt used. This study reports, to the best of our knowledge, the first conditions for the use of the putative azidoiodinane **7** at room temperature and could set precedent for the use of ammonium salts as sources of nucleophiles in hypervalent iodine chemistry.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data of all α-azido compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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