

A Stable and Safe Form of Iodine Azide: Polymer-Bound Bisazidoiodate(I)

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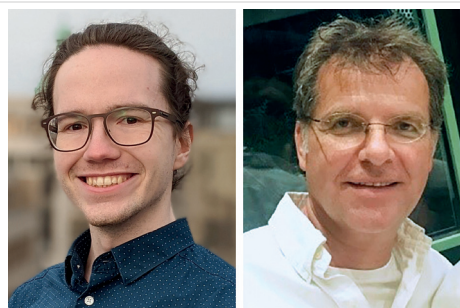
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Abstract **Key words** azides, iodine azide, oxidation, polymer-bound reagents, radical reaction

While haloazides like iodine azide have been known for many years, their use in synthetic organic chemistry has been considered challenging due to their unstable or even explosive nature.¹ Due to the extraordinary versatility of these interhalogen reagents for synthetic chemistry, there is a fundamental demand for safe and easy-to-use substitutes.

Although IN_3 can be generated *in situ* from iodine chloride and sodium azide in polar solvents,² this method and similar routes from TlN_3 ³ or Bu_3SnN_3 ⁴ have not gained wide acceptance. A safe route for the formation of IN_3 in the form of a stable analogue, the bisazidoiodate(I) complexes **3** or **3'**, which can be generated from organic iodide sources such as tetraalkylammonium iodide **1'** or basic ion-exchange resin in the iodide form **1**.^{5–10} The first step represents the oxidation of iodide, mediated by iodine(III) reagents, and the resulting iodate(I) complexes **2** or **2'** are then subjected to a ligand exchange reaction with Me_3SiN_3 to form the bisazidoiodate(I) complexes **3** or **3'** (Scheme 1).¹¹ While the ammonium-bound complex must be prepared *in situ*, a polymer-assisted version can be prepared on a large scale and stored for several months under argon atmosphere at -15°C without loss of activity. The polymer¹² did not exhibit explosive properties in impact experiments. Reactions with these functionalized polymers can be terminated by simple filtration. Active reagents remaining in solution can subsequently be removed by workup with thiosulfate-loaded ion-exchange resin **5**, eliminating the need for aqueous workup. Filtered polymeric byproducts such as **4** can be

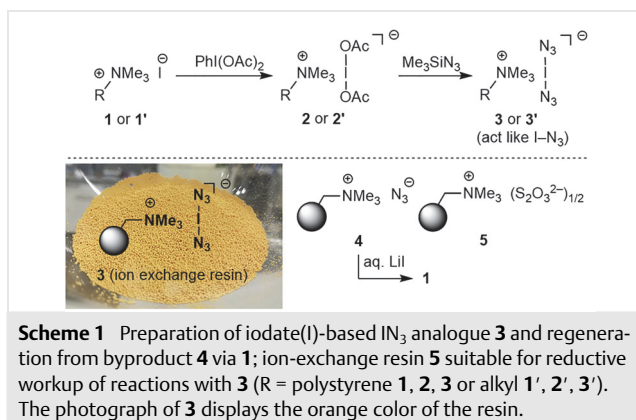


Vincent George studied chemistry at Leibniz University in Hannover (Germany) and received his master's degree in chemistry in 2021 after an Erasmus stay in Prague (Czech Republic), which was part of his master's studies on drugs and natural products. During his master's thesis studies under the supervision of Prof. Dr. Andreas Kirschning, he explored new reaction conditions for the safe generation of bromine azide with versatile applications in radical reactions.

Andreas Kirschning studied chemistry at the University of Hamburg and at Southampton University (UK). In Hamburg, he joined the group of Prof. Ernst Schaumann and received his PhD in 1989. After a post-doctoral stay at the University of Washington (Seattle, USA) with Prof. Heinz G. Floss, he started his independent research at Clausthal University of Technology in 1991, where he finished his habilitation in 1996. In 2000 he moved to the Leibniz University Hannover. His research interests cover structure elucidation as well as the semi-, muta- and total synthesis of natural products, complemented with the use of terpene synthases as synthetic tools. Other important aspects of his research deal with drug targeting and release and the development of synthetic technologies (solid-phase-assisted synthesis, microreactors, and inductive heating). Recently, he initiated a research program on the role of coenzymes and cofactors being involved in the origin of life.

used to recover the iodide loaded exchange resin **1** from where polymer-bound reagent **3** can be regenerated.^{1,2}

It has been suggested that iodine azide is released into solution from the polymer-bound bisazido iodate(I) complex **1** into the organic solvent of choice. There it can undergo a variety of reactions under well-controlled conditions. With alkenes, 1,2-addition is usually observed, yielding the corresponding 2-iodoazides. Noteworthy, these reactions tolerate various other functional groups and, in combinations with other functionalized polymers such as polymer-bound 1,8-diazabicyclo (5.4.0)undec-7-ene (DBU) **6**, could



be used as chemically active fixed-bed materials inside flow reactors (Table 1, **A**).

If these reaction mixtures are irradiated with light, e.g., using blue LEDs, a drastically changed reactivity is observed. Iodine azide is then no longer characterized by the electrophilicity of iodine, but radicals now dominate the reaction events. This includes the formation of radical addi-

tion products. Problems arising from the photoinstability of the carbo-iodine bond formed can be circumvented by addition of a stable radical scavenger such as (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO). This results in azido-oxygenated products from alkenes. In contrast, sterically very demanding substrates are oxidatively converted into bisazido adducts (Table 1, **B**).

In this way, iodine azide can not only be added to double bonds, but the photochemically generated azide radical can abstract hydrogen atoms from secondary alcohols to form intermediate ketyl radicals. The second H-abstraction then terminates the oxidation of the secondary alcohol and ketones are formed. The chemoselectivity of this oxidation is particularly noteworthy because it leaves primary alcohols unaffected (Table 1, **C**).

Under forcing conditions, however, primary alcohols also react, presumably to form aldehydes, which then undergo further H-abstraction under the photochemical conditions, and in that case the acyl radical is scavenged by the N_3 radical and acyl azides are formed, which further rearrange to the carbamoyl azide by Curtius rearrangement (Table 1, **D**).

Table 1 Applications of Polymer-Bound Bisazidoiodate(I) Complex **3** and a Stable Form of IN_3 ¹³

<p>(A) The addition of $\mathbf{3}^{13}$ to alkenes will result in electrophilic addition, forming the 1,2-<i>anti</i>-iodoazidated product. A large variety of functional groups, such as alcohols, nitro groups, and pyridines, is tolerated.² The conditions can even be used to functionalize glycals with good yields, giving glycosyl azides.³ Further treatment with non-nucleophilic bases such as DBU can induce the elimination of hydrogen iodide towards the newly introduced azide group. This was reported for a telescoped flow protocol.^{4,5}</p>	<p>Flow protocol:</p>
<p>(B) The addition of iodate(I) complex $\mathbf{3}^{13}$ to alkenes under irradiation conditions using blue LEDs results in the formation of the 1,2-bisazido addition product. However, the intermediate C-radical formed can be trapped with TEMPO to furnish the <i>anti</i>-azido-oxygenated product.¹ Sterically demanding alkenes preferentially still furnish 1,2-bisazides under these conditions.</p>	<p>But:</p>

(C) Ion-exchange resin 3 can also be used to oxidize secondary alcohols in the presence of primary ones with good yields and high selectivity. ^{1,13}	
(D) In the absence of secondary alcohols, primary alcohols can be oxidized under forcing conditions with blue LED irradiation forming the carbamoyl azide. The reaction is proposed to proceed via ketyl radicals and acyl azides that undergo Curtius rearrangement. Consequently, aldehydes are converted into the corresponding acyl azides. However, if the mixture is heated instead of being exposed to irradiation, the Curtius rearrangement takes place forming the carbamoyl azide. ^{1,6,7,13}	
(E) Oxidation and trisazidation of <i>para</i> -substituted phenol derivatives are achieved with polymer 3 . ^{8,13} Exposure of phenol to 3 results in 2,4,6-trisiodophenol (not shown).	
(F) Ion exchange resin 3 ¹³ promotes the double α -functionalization of ketones. ⁸ Secondary α -positions will undergo monoazidation.	
(G) Benzyl ether can be converted into azido ethers. ^{7,9} It was noted that greater yields could be achieved by substituting 3 with a mixture of $\text{PhI}(\text{OAc})_2$ and TMSN_3 or by directly using IN_3 . ^{9,10,13}	

In addition, polymer-bound bisazidoiodate(I) **3** provides a phenol-oxidation chemistry more familiar with iodine(III) compounds. *para*-Substituted phenol derivatives can be transformed into the trisazidation adduct at room temperature in very good yields (Table 1, **E**).

Finally, activated positions such as benzylic or α -carbonyl positions can be azidated when heated in the presence of the functionalized polymer **3** (Table 1, **F** and **G**).

In summary, bisazidoiodate(I) complexes enable a variety of diverse reactions and functionalizations that include alkene bifunctionalizations, alcohol and phenol oxidations. As a polystyrene-supported reagent, it offers additional advantages over homogeneous reagents in terms of stability, ease of workup, recycling (see Scheme 1), and thus reduction of waste. Due to its highly increased safety profile compared to iodine azide, a broader use of reagent **3** can be expected in the future, which will reveal additional reactivity of the very versatile interhalogen reagent IN_3 .

Conflict of Interest

The authors declare no conflict of interest.

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- Preparation of Polymer-Bound Bisazidoiodate(I) **3****
Amberlyst® A26 resin (4.2 mmol/g hydroxide form) was sequentially rinsed with 1 M NaOH (4 mL g⁻¹ polymer), saturated LiI solution (5 mL g⁻¹ polymer), distilled water (4 mL g⁻¹ polymer), isopropanol (4 mL g⁻¹ polymer), and CH₂Cl₂ (4 mL g⁻¹ polymer). A suspension of this polymer and $\text{PhI}(\text{OAc})_2$ (1.8 equiv) was shaken in dry CH₂Cl₂ (3 mL g⁻¹ resin) at 665 rpm for 6 h at room temperature under an argon atmosphere. During this time, the reaction mixture was protected from light. The pale-yellow resin **2** was filtered, washed with CH₂Cl₂ (30 mL g⁻¹ resin), and dried *in vacuo*. The polymer can be stored for several

months under argon atmosphere at $-15\text{ }^{\circ}\text{C}$ in the dark without loss of activity. Subsequently, a suspension of this functionalized ion-exchange resin **2** ($4.2\text{ mmol anion g}^{-1}$ resin, 1.0 equiv) and trimethylsilyl azide (2.6 equiv) in dry CH_2Cl_2 (4 mL/g resin) was shaken at 665 rpm for 6 h at room temperature in the absence of light under an argon atmosphere. The orange resin **3** was filtered, washed with CH_2Cl_2 (30 mL g^{-1} resin), and dried *in vacuo*. In practice, an effective loading of up to 2.1 mmol of

reagent g^{-1} of resin can be achieved. It can be stored for several months under argon atmosphere at $-15\text{ }^{\circ}\text{C}$ in the dark without loss of activity.

- (12) It is worth noting that polymer **3**, after being evaluated as safety, was commercially available for several years in the early 2000s.
- (13) Note: The number of equivalents for **3** refers to the theoretical loading as specified by the manufacturer of the ion-exchange-resin. The actual amount of IN_3 available is much less, therefore the number of equivalents does not describe the true ratio.