



*Citation for published version:*

Cresswell, A & Askey, H 2023, Tetrabutylammonium azide. in A Charette, J Bode, T Rovis & R Shenvi (eds), *Encyclopaedia of Reagents for Organic Synthesis*. Wiley. <https://doi.org/10.1002/047084289X.rn01686.pub2>

*DOI:*

[10.1002/047084289X.rn01686.pub2](https://doi.org/10.1002/047084289X.rn01686.pub2)

*Publication date:*

2023

*Document Version*

Peer reviewed version

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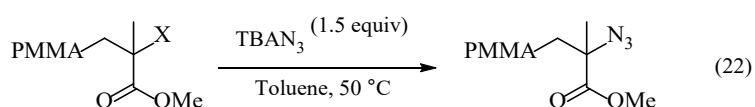
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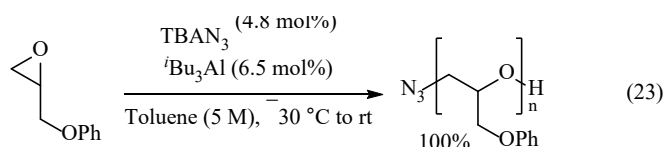
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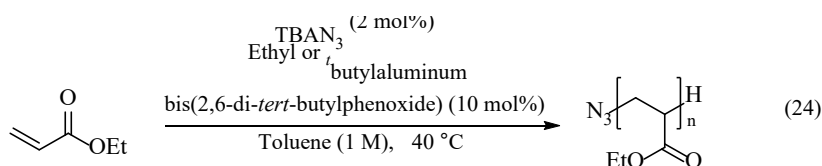
**Nucleophilic Azidation of Alkyl Halides.** The synthesis of alkyl azides commonly uses  $\text{NaN}_3$  for the nucleophilic substitution of alkyl halides in polar solvents (e.g. DMF, DMSO). This method can be used to prepare azido-end polyacrylates and polystyrenes. However, polymethacrylates suffer from poor  $\text{S}_{\text{N}}2$  reactivity due to the tertiary alkyl chain end, requiring a large excess of  $\text{NaN}_3$  and long reaction times for quantitative azidation. An alternative method, using  $\text{TBAN}_3$  in a non-polar solvent (toluene) has been developed, allowing nearly quantitative azidation of halide-end polymethacrylates with no large excess of azide (eq 22).<sup>19</sup>



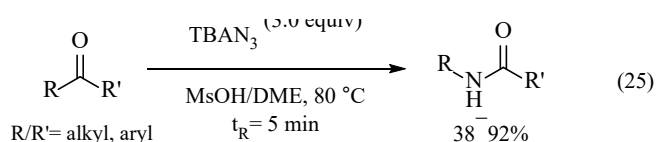
**Initiation of Anionic Polymerization.**  $\text{TBAN}_3$  can initiate anionic ring-opening polymerization for the synthesis of linear poly(glycidylphenyl ether), and the resultant azide terminus can subsequently be derivatized *via* the copper-catalyzed alkyne-azide cycloaddition ‘click’ reaction. The presence of Lewis acid *i*- $\text{Bu}_3\text{Al}$  during polymerization improved the end-group fidelity of the polymer chains, with azide ion opening the oxirane ring at the  $\alpha$ -position (eq 23).<sup>20</sup>



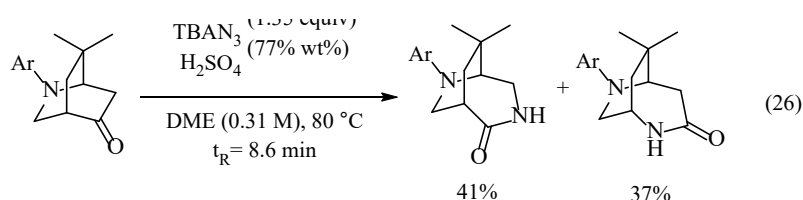
Similarly,  $\text{TBAN}_3$  can be used to initiate the anionic polymerization of ethyl acrylate in the presence of alkyl-aluminium bisphenoxides, enabling the synthesis of azide-terminated poly(meth)acrylates for macrocycle synthesis *via* ‘click’ chemistry (eq 24).<sup>21</sup>



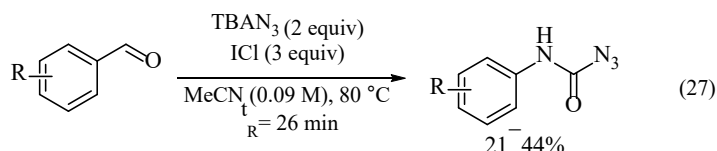
**Schmidt Reaction.** The Schmidt reaction, which enables *N*-insertive synthesis of secondary amides from ketones, typically uses NaN<sub>3</sub> under acidic conditions to generate hazardous hydrazoic acid (HN<sub>3</sub>) *in situ*. By virtue, flow chemistry offers a safer method for utilising HN<sub>3</sub> in synthesis, given that it may be generated and consumed in small quantities in a continuous manner, without accumulation. However, the poor solubility of NaN<sub>3</sub> in many organic solvents provides an impetus for the use of TBAN<sub>3</sub> as an organic-soluble azide source in such applications, including Schmidt reactions in flow. Thus, the conversion of a range of cyclic and acyclic ketones to their corresponding amides can be achieved in DME using a continuous flow microreactor (eq 25).<sup>22</sup>



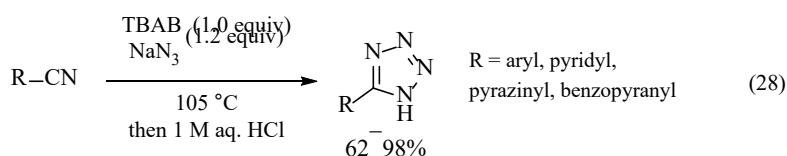
Similarly, a Schmidt rearrangement using TBAN<sub>3</sub> in continuous flow has been used as a ring expansion strategy for the synthesis of a bicyclic homopiperazine, although poor regioselectivity of the nitrogen insertion was observed (eq 26).<sup>23</sup>



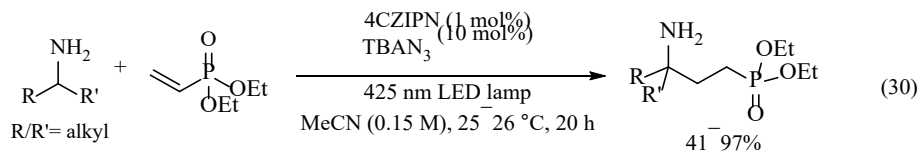
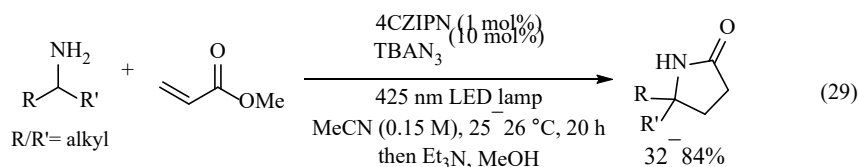
**Synthesis of Iodine Azide.** Iodine azide (IN<sub>3</sub>) is a synthetically valuable but highly toxic and explosive reagent. However, it can be safely generated *in situ* from TBAN<sub>3</sub> and iodine monochloride (ICl) using continuous flow microreactors, where it has been used for the synthesis of carbamoyl azides from aldehydes.<sup>24</sup> Initial reaction of IN<sub>3</sub> with aldehydes generates acyl azide intermediates, which undergo Curtius rearrangement upon heating to give isocyanates. Trapping of these isocyanates by excess azide ion delivers the carbamoyl azide products (eq 27).



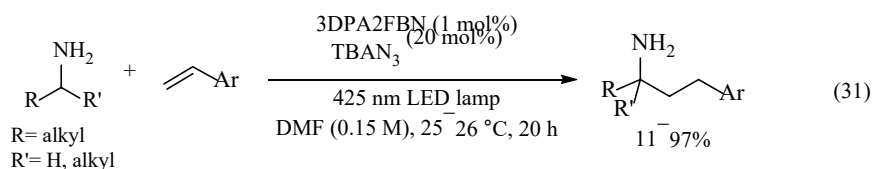
**Tetrazole Synthesis.** 5-Substituted 1*H*-tetrazoles can be accessed *via* the 1,3-dipolar cycloaddition of nitriles with azide ion, followed by acidification to neutralise the tetrazole anion. A solvent-free modification of this process with NaN<sub>3</sub> has been demonstrated using molten tetrabutylammonium bromide (TBAB) as the reaction medium, in which the *in situ* formation of TBAN<sub>3</sub> serves to bring azide ion into the melt phase. This procedure afforded a range of 5-(hetero)aryl-substituted 1*H*-tetrazoles, although alkyl aldehydes proved unsuccessful (eq 28).<sup>25</sup>



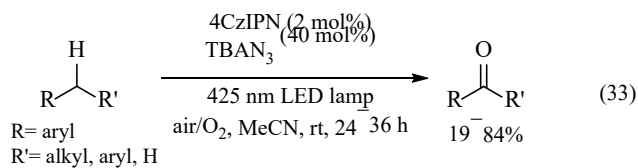
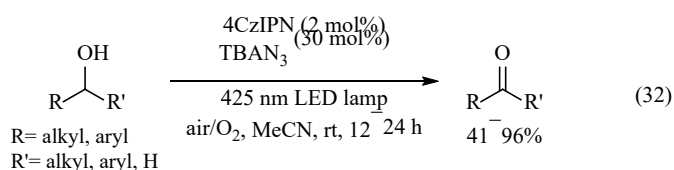
**C(sp<sup>3</sup>)-H Functionalizations and C=C Oxidations with Azidyl Radical.** TBAN<sub>3</sub> can serve as an organic-soluble precursor to the azidyl radical (N<sub>3</sub><sup>•</sup>), which may be generated under photo- or electrooxidative conditions. This highly electrophilic radical species can engage readily with nucleophilic C-H or C=C bonds, and reactions that are catalytic in azide ion are possible. For example, TBAN<sub>3</sub> has been deployed as a hydrogen atom transfer (HAT) catalyst in the photoredox-catalyzed α-C-H alkylation of unprotected primary alkylamines, in which α-amino radicals are formed as key intermediates. Capture of the latter radicals with acrylates, followed by post-reaction lactamization, affords a direct synthesis of α,α-disubstituted (including spirocyclic) γ-lactams (eq 29).<sup>26</sup> A similar reaction using vinyl phosphonates as radicophiles can be used to synthesize γ-aminophosphonates (eq 30).<sup>27</sup>



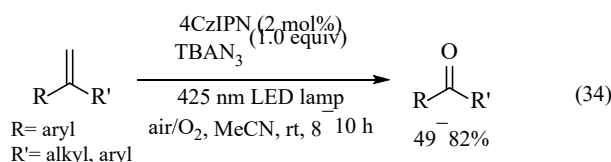
This chemistry can also be extended to non-electrophilic styrenes as radical acceptors, enabling a catalytic synthesis of unprotected  $\gamma$ -aryl primary amines (eq 31).<sup>28</sup> In all of the above C–H alkylation reactions, TBAN<sub>3</sub> was found to greatly outperform more commonly used HAT catalysts such as quinuclidine and tri(isopropyl)silanethiolate.



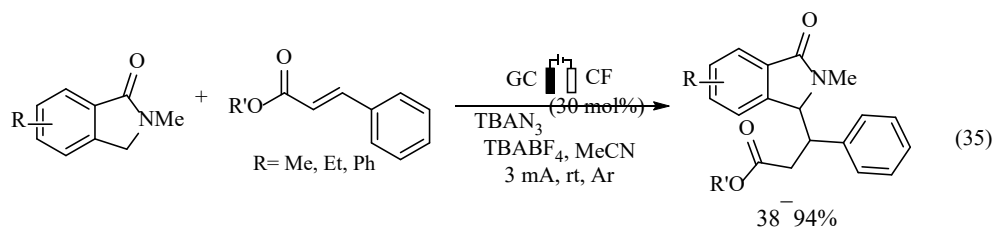
Hydrogen atom transfer catalysis with azide ion from TBAN<sub>3</sub> has also been exploited in the photoredox-catalyzed oxidation of alcohols (eq 32) and alkylarenes (eq 33) to give ketone (or aldehyde) products.<sup>29</sup> C–H abstraction by N<sub>3</sub><sup>•</sup> followed by capture of the carbon-centred radicals with O<sub>2</sub> are key mechanistic steps in these processes.



$\alpha$ -Substituted styrenes were also viable substrates in this ketone-forming process, albeit with stoichiometric TBAN<sub>3</sub>, providing a practical alternative to ozonolysis (eq 34).<sup>29</sup> Here, addition of N<sub>3</sub><sup>•</sup> to the C=C bond was envisaged to precede radical capture with O<sub>2</sub>, although the precise mechanism of ketone formation is unclear.



Azidyl radical formation from TBAN<sub>3</sub> can also be achieved electrochemically *via* anodic oxidation, and this strategy has been used for the  $\alpha$ -C–H amidoalkylation of  $\gamma$ -lactams, with various radical acceptors such as cinnamates, acrylates, and acrylonitrile (eq 35). Again, the N<sub>3</sub><sup>•</sup> radical is thought to activate the  $\alpha$ -C–H bond by hydrogen atom transfer, with HN<sub>3</sub> reacting at the cathode to evolve H<sub>2</sub> gas and regenerate the azide ion catalyst. *ortho*-Divinyl arenes were also exemplified as suitable radical acceptors, leading to spirocyclic scaffolds *via* tandem, sequential inter-intramolecular addition.<sup>30</sup>



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