SYNLETT
Spotlight 227

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Tetramethylguanidinium Azide (TMGA) – A Versatile Azidation Agent

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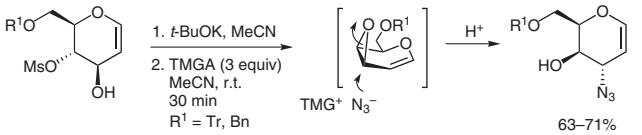
Introduction

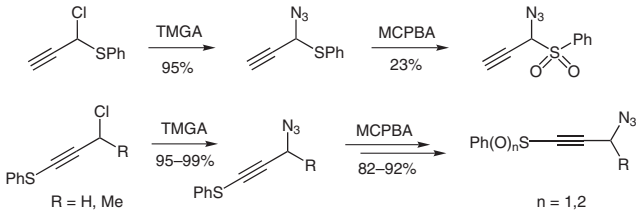
Organic azides have been widely used in synthesis, especially for the construction of heterocyclic systems, and as precursors of the primary amino group.[1] One method to incorporate the azide moiety into organic compounds is to use tetramethylguanidinium azide as the azidation agent. Tetramethylguanidinium azide (TMGA, $TMGN_3$) introduced by Papa[2] is commercially available, stable, nontoxic, and safe in use.[3] TMGA is a colorless hygroscopic solid, which is soluble in organic solvents (chloroform, dichloromethane, acetonitrile, nitromethane, DMF, acetone) and water; it is insoluble in diethyl ether and THF. The standard procedure for the preparation of TMGA involves the action of hydrazoic acid (HN_3) on tetramethylguanidine in ether.[2] The use of TMGA allows the introduction of the azido group under very mild non-aqueous conditions; however, it is not recommended to use halogenated solvents because explosive azidomethane species may be formed during the reaction.[3,4] TMGA is frequently used as a source of azide, in nucleophilic addition, substitution, azidolysis of epoxides, and heterocyclic ring formation.[5] It has been successfully used for the synthesis of alkyl,[2] alkenyl,[6] propargyl,[7] heteroaryl,[8] acyl,[9] phosphinic,[10] and sulfonyl azides[11] as well as for the preparation of *tert*-butyl azidoformate,[12] tetrazoles,[13] β-azido alcohols,[14] α-azido ketones[15] and α-amino acid derivatives.[16]

Abstracts

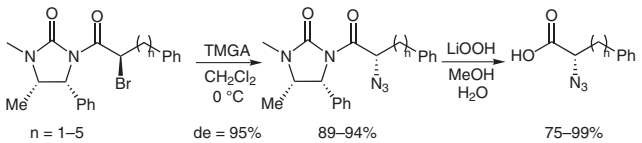
(A) The nucleophilic ring opening of in situ formed D-glucal-derived allylic epoxides with TMGA proceeds in a 1,2-regio- and *anti*-stereoselective way.[14b–c] The noncoordinating nature of the counterion (TMG^+) makes the epoxide react with the azide (N_3^-) in a noncoordinated fashion, necessarily at the C-3 oxirane carbon, affording the completely regio- and stereoselective result.[14b]



(B) Propargyl azides containing 1- or 3-phenylthio functionalities were prepared by the reaction of the corresponding propargyl chlorides with TMGA. The selective oxidation of their sulfur atoms to sulfoxides and sulfones allows access to the propargyl azides bearing acceptor substituents. Sulfur-containing propargyl azides were successfully used for the synthesis of allenyl azides, 1,2,3-triazoles, bis(triazolo)pyrazine derivatives, and substituted vinyl azides.[7] Acceptor-substituted propargyl azides were also converted into open-chain 1,2-diazidoethenes by one-pot reactions with TMGA.[6b]



(C) α-Bromoacyl imidazolidinones react with TMGA to give, after auxiliary cleavage, α-amino acid derivatives in excellent yields and diastereoselectivities.[16c] Similar methodologies (using oxazolidinones instead of imidazolidinones as chiral auxiliaries) were used for the asymmetric synthesis of many unusual α-amino acids.[16a–b,d]



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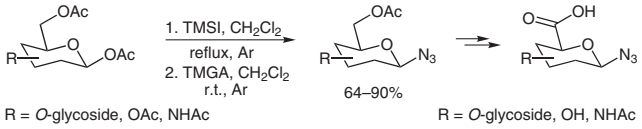
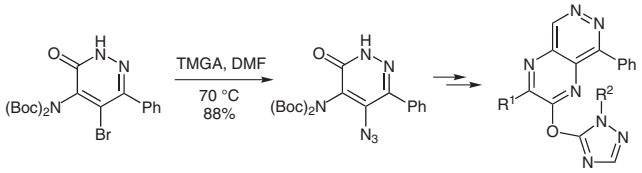
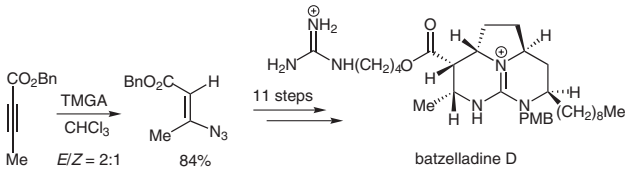
(D) TMGA is a versatile reagent for the stereoselective azidation of glycosyl derivatives.[3,17] Per-O-acetylated D-glycopyranoses were first converted into glycosyl iodides, followed by the reaction with TMGA to give β-D-glycosyl azides stereoselectively after deacetylation.[17a] β-Glycopyranosyl azides were next oxidized to glycopyranosyluronic acid azides.



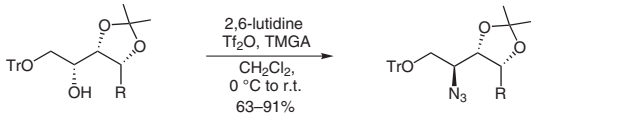
(E) Mitchinson and co-workers described the displacement of the bromine atom in the pyridazinone derivative using TMGA in DMF. The azide-substituted pyridazinone was next used for the preparation of 2,3,5-trisubstituted pyrazino[2,3-*d*]pyridazines, which are novel classes of $GABA_A$ receptor benzodiazepine binding-site ligands.[18]



(F) Gin and co-workers reported an elegant [4+2] annulation of vinyl carbodiimides with *N*-alkyl imines that resulted in a concise synthesis of batzelladine D, a marine guanidine alkaloid. The synthesis commenced with the addition of an azide derived from TMGA to 1,4-but-2-ynoic acid benzyl ester to give the β-azido acrylate in 84% yield (*E*/*Z* = 2:1).[19]



(G) Introduction of an azide group by a one-pot triflate activation of the free hydroxyl group, followed by azidation with TMGA, has been recently applied for the construction of phytosphingosine and α-galactosyl ceramide[20] as well as for the synthesis of glycaro-1,5-lactams and tetrahydrotetrazolopyridine-5-carboxylates.[21]



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