The Banert Cascade: A Synthetic Sequence to Polyfunctional NH-1,2,3-Triazoles

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Abstract: A series of polyfunctional NH-1,2,3-triazoles were prepared directly from propargyl halides and nucleophiles using a powerful, albeit little appreciated, synthetic sequence we call the Banert cascade. Propargyl azides, prepared in situ from propargyl halides or sulfonates, underwent a thermal rearrangement sequence to triazafulvene intermediates, potent electrophiles, which were readily captured by diverse nucleophiles. Using this cascade, a series of racemic azidomethyl(hydroxymethyl)-NH-1,2,3-triazoles were prepared by a two-step protocol that commences with the addition of propargyl chloride to aldehydes and ketones.

Key words: triazoles, heterocycles, azides, rearrangements, alkynes, cyclizations, Banert cascade

Compounds containing the N-unsubstituted 1,2,3-triazole heterocyclic moiety A are less common than their substituted analogs B (Figure 1). Nevertheless, A is found in molecules of significant biological interest, such as protease inhibitors, anticancer agents, non-steroidal antiinflammatories and potassium channel activators. Thus, these pathways are limited in scope when targeting functionalized NH-triazoles.

In 1989, Klaus Banert disclosed an extraordinary new path to NH-triazoles. His process is remarkable, not only conceptually, but also in its reliability and scope as it provides access to functionalized NH-triazoles under very mild conditions. Banert’s discovery revealed that substituted propargyl azides undergo a [3,3]-sigmatropic rearrangement to yield short-lived allenyl azides that readily cyclize to triazafulvene intermediates (Scheme 1). The intermediate triazafulvenes, with calculated dipole moments greater than 5 Debye, are quickly trapped by nucleophiles to furnish triazoles bearing benzylic functionality. The demonstrative reactions were performed in methanol or aqueous media with the dissolved nucleophilic additives, azide, ammonia and 2-propanethiol. Even though the involvement of the triazafulvene intermediate was unprecedented and could not be directly observed, mechanistic evidence strongly points to the cascade sequence shown in Scheme 1 and is not consistent with a simple azide–alkyne cycloaddition in concert with nucleophilic substitution, a conceivable alternate pathway.

A literature search yields just one cited application of this NH-triazole synthesis. Chemists at Merck Research Laboratories used it in the course of structure–activity relationship studies on analogs of a previously known human neurokinin-1 (h-NK1) receptor antagonist. Nevertheless, its utility has now found a real home in our laboratory as a nitrogen heterocycle stitching reaction and in many ways complements the copper-mediated ‘click’ reaction between organic azides and terminal alkynes. Our interest in this unusual transformation lies in its ability to produce covalent attachments in succession with heterocycle formation by way of the intermediate triazafulvene. Following the eponymous tradition of affiliating important reactions with their discoverers, we call this sequence the Banert cascade. Our aim, represented by the examples reported below, is to begin laying the foundation for viewing the Banert cascade as an inherently powerful synthetic protocol. It is already apparent that this reaction is general and reliable, as we have not yet found any major weaknesses in its scope. Herein we report our results on the preparation of polyfunctional NH-triazoles containing azidomethyl- and hydroxymethyl-NH-triazole moieties from aldehydes and ketones.

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Our initial efforts to employ the Banert cascade began by optimizing a modified set of existing conditions using propargyl chloride (1a) as the model substrate, azide as a prototypical nucleophile and ammonium chloride as a buffering agent (Scheme 2). Screening a variety of solvents, which included water, dimethyl sulfoxide, acetone, dimethylformamide and dioxane, gave insight to product formation dependency. On water, the reaction proceeded with complete consumption of starting material but afforded only polymeric products. Since 1a is insoluble in water and is effectively neat under these conditions, any triazole product that forms is nucleophilic enough to intermolecularly attack the triazafulvene intermediate, thus resulting in polymer. In dimethyl sulfoxide, the reaction halted at propargyl azide (1b) and despite the elevated temperatures did not yield any triazole product 2. Acetone and dimethylformamide gave mixtures of undesired side products with only small quantities of 2, as observed by TLC, and were not explored further.

Scheme 2 Preparation of compound 2 was ultimately successful in mixtures of dioxane–water. However, at high water content (dioxane–water, ratio 1:3) 1a was marginally soluble, plagued the reaction with significant polymeric byproduct formation. Adjusting the ratio of dioxane–water to 3:1 afforded 2 in 92% isolated yield after passing the crude product through a short silica plug.

To determine whether the buffered dioxane–water (3:1) conditions optimized for 2 were applicable to other substrates, a group of readily accessible propargyl halides and sulfonates were converted into the corresponding azidomethyl-NH-triazole adducts 3a–i (Scheme 3). In all cases, the products were obtained in moderate to high yields following aqueous workup and purification by recrystallization or chromatography. The yields were nearly constant for neighboring alkyl, aryl and phthalimide substituents (entries 1–4, 6 and 8, Scheme 3). When using just the one equivalent of sodium azide to form the propargyl azide, water was nucleophilic enough to yield the corresponding hydroxymethyl-NH-triazole 3d.18 Butynol did not compete as a potential inter- or intramolecular nucleophile (3e). When 1,4-dichloroethyne was subjected to the standard conditions, bisazidomethyl-NH-triazole (3g) was isolated in a 60% yield, which must originate from 1-azido-4-chloroethyne as the rearranging precursor, since the only noticeable byproduct, 2,3-diazido-1,3-butadiene, is known to be the exclusive thermodynamic end point of 1,4-diazidoethyne.19 Even though 3g could be fully characterized, attempts to crystallize it were not made; instead, 3g was treated with p-nitrobenzenesulfonyl chloride (NsCl) and potassium carbonate in toluene at room temperature to yield 2-Ns-4,5-bisazidomethyl-1,2,3-triazole as a stable crystalline solid (see experimental section for characterization).

Compound 3i typifies the attachment of a parent methyl-NH-triazole unit to azide anion by way of propargyl azide (4),20 prepared in situ from prop-2-ynyl methanesulfonate (propargyl mesylate).21 With this precursor, a variety of amine and thiol containing compounds were examined as nucleophiles for preparing compounds representative of 5 (Scheme 4). Treatment of propargyl mesylate with one equivalent of sodium azide at room temperature afforded a solution of 4, which was subsequently heated with the desired nucleophile. Mercaptopyr dine reacted cleanly under these conditions to afford the desired thio ether 5a.
in good yield; the only byproduct being the disulfide of residual nucleophile, which was easily separable. Secondary amines also underwent clean transformation to the corresponding aminomethyl-NH-triazole (5b). However, a primary amine afforded the desired product 5c in lower isolated yield since the resulting aminotriazole is a competent nucleophile capable of reacting with the triazafulvene intermediate, producing bis-NH-triazole contaminants. By limiting the stoichiometry of the primary amine to one-half equivalent, bis-NH-triazoles 5d, e were isolated in acceptable yields, demonstrating a facile route to tridentate chelating compounds. Phenols and their sodium phenoxide salts were incompatible with the model conditions and phenolic ethers such as 5f were not formed.

The preparation of substituted 4-azidomethyl-5-hydroxymethyl-NH-triazoles, reminiscent of compound 3e, was achieved by a two-step sequence starting from aldehydes and ketones (Scheme 5). Treatment of propargyl chloride with n-butyllithium in diethyl ether22 followed by addition of either an aldehyde or ketone afforded racemic chlorobutynol triazole precursors 6 upon aqueous work-up, which were used without purification.

Scheme 3 Reaction conditions: propargyl-X (1.0 equiv), NaN₃ (4.0 equiv), NH₄Cl (2.0 equiv), dioxane–water (3:1) at 75–80 °C, 6–8 h. * Isolated yields after purification. b Only one equivalent of NaN₃ added.
Subsequent treatment with excess buffered sodium azide in dioxane–water (cf. reaction conditions described for Scheme 3) gave the corresponding polyfunctional NH-triazoles in moderate to good yields over two steps (7a–j). Alternatively, this transformation could be performed in one-pot by simply quenching the initial reaction with aqueous ammonium chloride and heating the resulting mixture with sodium azide and dioxane. This protocol was required for 2-furaldehyde (entry 1, Scheme 5) whose chlorobutynol intermediate was unstable and decomposed after standard workup. The transferability of these reaction conditions across the selected series of substrates chosen for Scheme 5 demonstrates that this method is applicable to the synthesis of related aldehyde and ketone derivatives that tolerate the addition of lithiated propargyl chloride and the presence of sodium azide at elevated temperatures. Furthermore, existing methods for the asymmetric addition of terminal alkynes to carbonyls\textsuperscript{23} may give rise to enantiomerically enriched hydroxymethyl-NH-triazoles.

In summary, the thermally induced rearrangement of propargyl azides, the Banert cascade, bears the name of its pioneer and has been established as an efficient method for the preparation of NH-triazoles containing adjacent azido- and hydroxymethyl substituents from aldehydes and ketones. We have expanded the group of nucleophiles that participate in the covalent attachment to triazafulvene intermediates and have devised a convenient method for the addition of methyl-NH-triazoles to amino and thiol cores with in situ prepared propargyl azide. The compounds prepared via this protocol are representative of a much larger class of building blocks that will be instrumental for 'click' chemistry exploration. Additionally, the resulting azidomethyl-NH-triazoles and their propargyl azide precursors are currently being examined in biological settings for enzyme inhibition\textsuperscript{14} and selective protein profiling.\textsuperscript{24}

\textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded on Varian (Inova 300 and 400 MHz) spectrometers with TMS as an internal standard. Mass spectrometry was performed on a Hewlett Packard Series 1100 MSD in positive total ion mode. All experiments were carried out.
open to the atmosphere, unless otherwise noted, in reagent grade solvents as supplied by Fischer Scientific Co. Commercial chemicals were used as supplied from Aldrich or Acros Chemical Co. Column chromatography was performed on silica gel (230–425 mesh). Melting points were determined on a Thomas Hoover Uni-Melt capillary melting point apparatus and are uncorrected.

**Scheme 5**  
*Reaction conditions:* (a) (i) propargyl chloride (1.0 equiv), BuLi (1.0 equiv), Et₂O, −78 °C, 10 min; (ii) aldehyde or ketone (0.95 equiv), Et₂O, −78 °C → r.t., then aq NH₄Cl; (b) NaN₃ (4.0 equiv), NH₄Cl (2.0 equiv), dioxane–water (3:1), 75 °C, 12 h. * Isolated yields over two steps after purification.

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**Thermally Induced Banert Cascade; Representative Procedures**

4-Azidomethyl-5-hydroxymethyl-NH-triazoles (3e)

To a solution of 4-chlorobut-2-yn-1-ol (0.50 g, 5 mmol) in dioxane–H₂O (3:1; 25 mL) was added sodium azide (1.25 g, 20 mmol) and NH₄Cl (0.51 g, 10 mmol). The reaction was stirred at 75 °C for 8 h. Subsequently the reaction was cooled to r.t. and partitioned between H₂O and EtOAc. The organic layer was separated and the aq layer
was extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried (MgSO₄), filtered, and evaporated to dryness. The crude oil was purified via a short silica column (silica gel; hexane–EtOAc, 1:2) to yield a clear viscous oil that solidified on standing to a crystalline solid. The solid was purified by chromatography (silica gel; hexane–EtOAc, 1:2) to yield a white precipitate.

Yield: 0.48 g (70%); mp 145–146 °C.

1H NMR (300 MHz, CDCl₃): δ = 5.20 (s, 1 H), 4.75 (s, 2 H), 4.54 (s, 2 H).

13C NMR (75 MHz, CDCl₃): δ = 143.6, 140.0, 55.1, 45.1.


4-Azidomethyl-5-hydroxymethyl-VH-triazoles from Aldehydes and Ketones; Representative Procedures

1-(3-Chloroprop-1-ynyl)indan-1-ol (6d)

To an anhyd solution of propargyl chloride (1.77 g, 24 mmol) in Et₂O (40 mL) at –78 °C was added BuLi (9.6 mL; 2.5 M solution in hexane) over 5 min. The solution was stirred for an additional 10 min at –78 °C and a r.t. solution of 1-indanone (2.64 g, 20 mmol) in Et₂O (20 mL) was subsequently added via cannula. The resulting solution was stirred at –78 °C for 1 h, warmed to r.t. and quenched with sat. aq NH₄Cl. The organic layer was separated and the aq layer was extracted with EtOAc (2 × 10 mL) at –78 °C. The resulting solid could be recrystallized from EtOAc to afford an off-white solid.

Yield: 3.5 g (86%); mp 78–79 °C.

1H NMR (300 MHz, CDCl₃): δ = 7.5 (d, J = 7 Hz, 1 H), 7.3 (m, 3 H), 4.2 (s, 2 H), 3.1 (m, 1 H), 2.9 (ddd, J = 15.0, 6.0, 4.0 Hz, 1 H), 2.8 (br s, 1 H), 2.6 (m, 1 H), 2.4 (ddd, J = 9.0, 6.0, 4.0 Hz, 1 H).

13C NMR (75 MHz, CDCl₃): δ = 145.0, 142.9, 129.0, 127.0, 124.9, 120.7, 118.4, 45.9, 40.0, 31.3.

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This product was anticipated based on the results described by Banert using methanol both as solvent and nucleophile.\textsuperscript{12a–c}


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