

Cationic 1,2,3-Triazolium Alkynes: Components To Enhance 1,4-Regioselective Azide–Alkyne Cycloaddition Reactions

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ABSTRACT: 4 Alkynyl 1,2,3 triazolium cations undergo thermal [3 + 2] cycloaddition reactions with azides roughly 50 to 100 fold faster than comparable noncharged alkynes. Further, the reaction is highly 1,4 regioselective (dr up to 99:1) owing to the selective stabilization of 1,4 TS transition states via conjugative π acceptor assistance of the alkyne triazolium ring. The novel cationic triazolium alkynes also accelerate the CuAAC reaction to provide bis(1,2,3 triazoles) in an “ultrafast” way (<5 min).

Enhancing the clickability¹ of the intrinsically sluggish and nonselective Huisgen² azide–alkyne [3+2] cycloaddition reaction (Figure 1, top) has resulted in some of the most versatile methods to connect molecules covalently through 1,2,3 triazole units. The Sharpless/Meldal copper(I) accelerated version of the reaction (CuAAC)³ and Bertozzi’s strain promoted cycloalkyne variation (SPAAC)⁴ are excellent examples of the transformation of such a reaction into a “click” process.

In order to avoid the biotoxicity of copper salts and the inherent instability and cumbersome synthesis of highly strained alkynes,⁵ several authors have proposed the use of electron deficient *o*-nitrophenylalkynes⁶ or propiolates⁷ to carry out copper free Huisgen reactions. Recently, Alabugin has developed this approach to activate nonstrained alkynes by stabilizing the reaction transition state via hyperconjugative assistance with propargylic electron withdrawing groups (Figure 1, bottom left).⁸ Although satisfactory reaction rate increases were attained in some instances, these cycloadditions displayed no or, at best, modest regioselectivity⁹ and were very limited in their substitution scope.

We surmised that robust cationic alkynes containing the 3-methyl 1,2,3 triazolium moiety¹⁰ could act as strong π acceptors in dipolarophiles toward donor azides providing highly activated cycloadditions suitable to overcome the aforementioned drawbacks (Figure 1, bottom right). To test our hypothesis, we first synthesized a variety of 4-ethynyl 1,2,3 triazoles **1** from azides following a standard CuAAC approach^{11,12} (Scheme 1) and achieved their N-methylation with the Meerwein salt Me₃OBf₄ or methyl triflate to obtain the desired triazolium alkynes **2** in good to excellent yields.¹³

With the triazolium alkynes in hand, we conducted a kinetic study to determine the reaction rates of the second order cycloaddition of benzyl azide **3a** with the neutral alkyne **1a** and cationic analogue **2a** (Table 1, top). The reactions were conducted in MeCN-*d*₃ at 80 °C, and the formation of each 1,4 and 1,5 isomer of the resulting bis-triazoles **4** and **5** was monitored by ¹H NMR (see SI, Figure S2). In agreement with our hypothesis, the cationic alkyne **2a** reacted with benzyl azide to afford the regioisomer **5**_{1,4} about 2 orders of magnitude

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faster than the neutral alkyne 1a to give 4_{1,4}. Surprisingly, regioisomer 5_{1,5} was formed only 4 fold faster than 4_{1,5} under identical conditions. As a result, cationic adducts 5 were obtained in an excellent 95:5 isomer ratio, whereas the neutral analogues 4 gave a roughly equimolar mixture. The Arrhenius activation energies (Table 1, $\Delta E_{\text{exp}}^{\ddagger}$) of the cycloadditions confirmed that N methylation of 1a to 2a caused a lowering of 6 kcal·mol⁻¹, which was in good agreement with the reaction rate increase observed experimentally. More significantly, the Eyring–Polanyi plots for each regioisomer showed a free energy difference ($\Delta\Delta G_{\text{exp}}^{\ddagger}$) of only 0.3 kcal·mol⁻¹ between the activation barriers of triazoles 4_{1,5} and 4_{1,4}, whereas such value increased to 2.1 kcal·mol⁻¹ for 5_{1,5} and 5_{1,4}. When the activation energies were measured in DMSO d₆, a destabilizing solvent effect of 3.2–2.8 kcal·mol⁻¹ relative to acetonitrile was recorded for the cationic alkyne 2a but not for the less polar 1a (SI, Table S3).

Next, we studied the cycloaddition reaction of cationic triazolium alkynes 2a and 2d with several azides 3 of variable electron density in acetonitrile at 80 °C (Table 2). In all instances, high yields and excellent 1,4 regioselectivities were attained irrespective of the azide used. Reaction rate constants $k_{1,4}$ were strongly dependent on the electron donating ability of the azide. For instance, azides (entries 2–4), typically

reacted 1 order of magnitude slower than aliphatic azides (entry 1), and the very electron rich bis(trimethylsilyl)methyl azide 3e (entry 5) reacted 100 fold faster than phenyl azide 3c. In contrast, reaction rate constants $k_{1,5}$ remained almost unaffected by the electronic nature of the azide in values close to 10⁻⁶ M⁻¹·s⁻¹ (SI, Figures S5 and S6). Finally, the cationic internal alkyne 2d also reacted with benzyl azide at 130 °C in toluene to afford the triazole 10 in a 90:10 regioisomer ratio, a much higher regioselectivity than attained in related cycloadditions.

In parallel with the kinetic determinations, we computationally explored the origin of the high regioselectivity observed for cationic alkynes 2. Ab initio calculations at the B3LYP/6-31+

+G** level of theory (MeCN solvent) using the Gaussian09 suite of programs yielded the four transition states shown in Figure 2 (top). Their activation Gibbs energies corrected to 80 °C were in good agreement with the experimental values (Table 1) and accounted for the activation free energy difference $\Delta\Delta G^{\ddagger}$ of about 2–3 kcal·mol⁻¹ between cationic TS 5_{1,4} and

TS 5_{1,5}, identical to the distortion energies (ΔE_{dis}) and formation energies (ΔE_{for}) and TS 4_{1,4} and TS 4_{1,5} (SI, Figure S8). Reaction activation energies over the distortion energy difference between 1,5 and 1,4 transition states was only 1.4 kcal·mol⁻¹ for neutral alkyne 1a and 4.2 kcal·mol⁻¹ for the cationic analogue 2a. Such an energy difference emerged mostly from the azide component. On the other hand, interaction energies released in electrostatic and frontier orbital interactions were very similar for each 1,4 /1,5 transition state pair, but their values were 6–8 kcal·mol⁻¹ more negative for TS 5_{1,4} and TS 5_{1,5}, in line with their charged electronic nature.

Finally, the structural and stereoelectronic characteristics of the transition states depicted in Figure 2 were examined. Although the formation of C–N bonds was appreciably more asynchronous for the transition states arising from the cationic alkyne 2a, the forming bond length differences could not be correlated with the observed 1,4 /1,5 regioselectivities. Much more meaningful was the comparison of the dihedral angles θ encompassing the N–C–C–N atoms between the two triazole rings in the transition states. Actually, all of them were essentially coplanar with the exception of TS 5_{1,5}, which was.

A fragment analysis of frontier molecular orbitals of TS 5_{1,4} and TS 5_{1,5} using the ADF software¹⁵ at an HF/DZ level of theory allowed the identification of the bonding orbital orthogonal

S9 and S10). The quantitative Kohn–Sham electronic structure analysis for the formation of the 1,2,3 triazole ring in TS 5_{1,4} yielded an expected coplanar approach of the azide (Figure 2, bottom, interaction A), stabilized through a conjugative π acceptor assistance (B). However, in the case of TS 5_{1,5}, such stabilization was canceled by the orthogonal disposition of HOMO_{azide} and LUMO_{alkyne} (approach C), and the alternative HOMO–1_{azide} and LUMO+1_{alkyne} approach was precluded by the steric hindrance between the azide substituent and the alkyne triazolium *N* methyl group. The absence of this obstacle in the uncharged TS 4_{1,5} accounted for the low regioselectivity observed during the cycloaddition of alkyne 1a.

Encouraged by the successful activation of thermal [3 + 2] cycloadditions achieved with cationic alkynes 2, we explored their use as components of copper catalyzed reactions. We anticipated that the strongly electron deficient triazolium moiety would stabilize the transition state D (Figure 3, top), which is the rate limiting step of the CuAAC catalytic cycle.¹⁶

Indeed, when the reaction of an equimolar mixture of alkynes 2b and 1b and benzyl azide 3a was catalyzed by 20 mol % of CuOAc/NaOAc, a totally chemoselective transformation occurred to give exclusively the adduct 11, leaving the alkyne 1b unchanged.¹¹ When the transformation was monitored by ¹H NMR from initial 35 mM solutions of the reagents at 27 °C, the conversion was complete in few minutes (SI, Figure S7).

Finally, the preparative scope of the methodology was checked for different azides. As shown in Table 3, “ultrafast” click reactions of triazolium alkynes were very efficient under the standard Sharpless conditions using 20 mol % CuSO₄/sodium ascorbate catalyst (entry 1). In addition, the metal load could be further reduced to 1 mol % without compromising the reaction performance using CuOAc as catalysts in the presence of 2 equiv of NaOAc.^{16b} The scope of the reaction included standard aliphatic azides (entry 1) and also poorly reactive aromatic azides with electron withdrawing groups (see entries 4 and 6). The reaction also worked efficiently for strongly hindered aromatic azides (see entries 7 and 8) and was tolerant with functionalized aliphatic azides (entries 9 and 10). Overall, this alkyne activated reaction proved highly efficient and suitable to complement alternative “ultrafast” CuAAC approaches based on copper chelating pyridyl azides.¹⁷

In conclusion, we have described a novel family of *N* methyl 1,2,3 triazolium cationic alkynes 2 displaying a very particular combination of electronic activation and punctual steric hindrance, both provided by the *N* methylation of 4 alkynyl 1,2,3 triazoles. We have also studied their [3 + 2] cycloaddition reaction with azides unveiling the mechanistic details underlying the simultaneous torquoselective like¹⁸ 1,4 activation and 1,5 deactivation through the corresponding transition states. This has permitted the development of a general, mild, and very 1,4 regioselective version of the Huisgen reaction. Cationic alkynes 2 have also been found to strongly accelerate the copper catalyzed reaction with azides providing unprecedented “ultrafast” CuAAC reactions that complete in very short reaction times (<5 min) and proceed with complete chemo selectivity in the presence of ordinary noncharged alkynes. Further studies are being conducted in our laboratory to extend the reactivity of cationic triazolium alkynes to other 1,3 dipoles and nucleophiles.

Preparation procedures; NMR spectra of compounds 1d, 2b, 4, and 4–19; determination of reaction rate constants and activation parameters, computational geometries, energies and fragment analysis for transition states TS 4_{1,4}, TS 4_{1,5}, TS 5_{1,4} and TS 5_{1,5} (PDF)

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