RSC Advances

PAPER

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Cite this: RSC Adv., 2017, 7, 47527

Experimental and theoretical studies of the [3,3]-sigmatropic rearrangement of prenyl azides†

Exequiel O. J. Porta,[a] Margarita M. Vallejos,[b] Andrea B. J. Bracca[a] and Guillermo R. Labadie*[ac]

Received 2nd September 2017
Accepted 3rd October 2017

DOI: 10.1039/c7ra09759j

rsc.li/rsc-advances

[3,3]-Sigmatropic rearrangement of isoprenyl azides has been extensively investigated in an experimental and theoretical level. Prenylazides with different chain lengths and phenyl prenylazide have been synthesized. NMR analysis of each azide has been made to determine the equilibrium composition, showing the predominance of primary allyl azides over the tertiary ones and *E* over *Z* isomer, regardless of the chain length, temperature, solvent or the regiochemistry of the precursor isoprenyl alcohol. It was determined that phenyl prenylazides do not experience [3,3]-sigmatropic rearrangement. In order to rationalize the experimental results and to gain insight in the mechanism of the [3,3]-sigmatropic rearrangement of prenylazides a theoretical study was performed using density functional theory and the QTAIM approach.

Introduction

In this century, an amazing increase in the number of applications of organic azide derivatives have been reported. Azides and alkynes chemical orthogonality has allowed unique applications in different fields including bioconjugation,[1] material sciences,[2] organic chemistry and medicinal chemistry.[3] 1,2,3-Triazoles synthesis became very valuable after the independent discoveries of Meldal's[4] and Sharpless'[5] groups that introduced the copper(I) accelerated Hüisgen 1,3-dipolar cycloaddition of alkynes and azides (CuAAC). That completely regioselective reaction has become one of the most commonly used organic synthesis.

Allylic azides are versatile building blocks for the synthesis of natural products and nitrogen-containing heterocycles of pharmacological relevance. However, they undergo a spontaneous dynamic rearrangement at ambient temperature (Fig. 1). In 1960 Young and co-workers reported the study of [3,3]-sigmatropic rearrangement of allylic azides (known as Winstein's rearrangement).[6] They observed that allylic azide exists as a regioisomeric mixture that interconverts rapidly at room temperature. Lately, VanderWerf and Heasley found that tertiary and secondary allylic azides rearrange faster than the primary ones[7] with the regioisomer with the most substituted alkene being thermodynamically favoured. The effective application of this reaction in synthetic schemes has been difficult due to the spontaneous rearrangement. It is necessary to control the thermodynamic ratio of the regioisomeric azides in order to be synthetically useful and that generally depends on the substrate.[8]

Isoprenylazides have been used for protein labelling[9] and to prepare 1,2,3-triazole libraries, generating phenyl triazoles **1** as antibiofilm,[10] steryl derivatives **2** as antiparasites,[11] bisphosphonates **3** as geranylgeranyl transferase II inhibitors[12] and β-lactones **4** as fatty acid synthase inhibitors (Fig. 2).[13] In those reports, prenyl azides in equilibrium reacted with alkynes to produce 1,2,3-triazoles as a mixture of regioisomers. Recently, our group has successfully prepared and chromatographically separated different regioisomers derived from prenyl-1,2,3-triazoles. The activity of those compounds is hardly dependent on the regiochemistry of the first isoprenic unit, playing an important role on the modulation of the activity between trypanosomatids.[14]

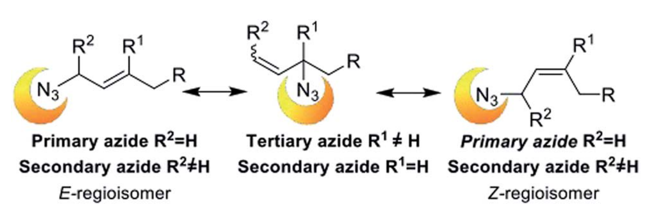


Fig. 1 [3,3]-Sigmatropic rearrangement of allyl azides.

[a]Instituto de Química Rosario, UNR, CONICET, Suipacha 531, S2002LRK, Rosario, Argentina. E-mail: labadie@iquir-conicet.gov.ar; Fax: +54-341-4370477 ext. 112; Tel: +54-341-4370477 ext. 108

[b]Laboratorio de Química Orgánica, IQUIBA-NEA, Universidad Nacional del Nordeste, CONICET, FACENA, Av. Libertad 5460, Corrientes 3400, Argentina

[c]Departamento de Química Orgánica, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 531, S2002LRK, Rosario, Argentina

† Electronic supplementary information (ESI) available: NMR spectra of all synthesized compounds. Distances, topological properties and electron population along the Cartesian coordinates of the stationary points under study. See DOI: 10.1039/c7ra09759j

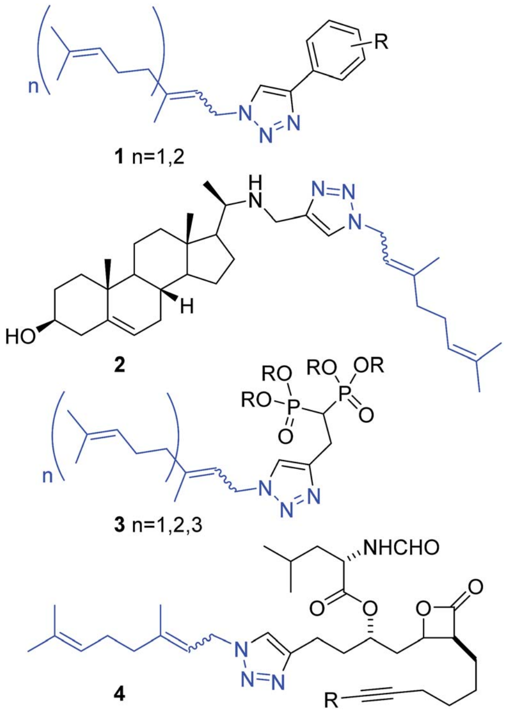
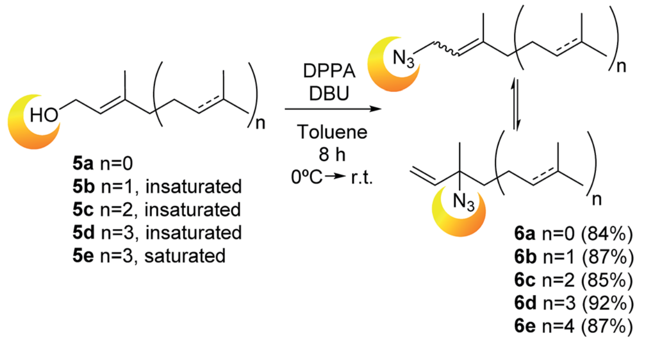


Fig. 2 Bioactive prenyl 1,2,3-triazole derivatives.



Scheme 1 Synthesis of prenyl azides **6a–e** from the corresponding alcohols (prenol, geraniol, farnesol, geranylgeraniol and phytol, respectively).

Besides the utility of this important scaffold, a complete study of the isoprenylazides equilibrium has not been conducted. That information will contribute to find factors that rule the equilibrium and the reactivity of this synthetically useful compounds. Therefore, in this paper we report a detailed experimental and theoretical study of isoprenylazides and their [3,3]-sigmatropic rearrangement.

Results and discussion

Chemistry

Synthesis. In recent years, numerous methods for the preparation of allylic azides by substitution reactions from allylic halides or (homo)allylic alcohols and metal-catalysed azidation have been reported.[15–23] However, allylic halides are very reactive species and are prone to decomposition. On the other hand, metal-catalysed reactions are very expensive. To avoid this problem, isoprenyl azides **6a–e** were conveniently prepared from the corresponding isoprenyl alcohols **5a–e** following the one-pot modified Mitsunobu procedure (Thompson's reaction), using diphenylphosphorylazide (DPPA) as azide donor and 1,8-diazabicycloundec-7-ene (DBU) as a non-nucleophilic base.[24,25] After 8 hours reaction, the allylic azide mixture are obtained with an average yield of 87% after purification (Scheme 1). This one-pot procedure enabled a clean and rapid preparation of the products due to the high lipophilicity of the product mixture, compared to the reagents.

All the attempts to obtain a single isomer from this mixture was doomed due to the dynamic interconversion. Presumably, the physicochemical properties are an additional factor that difficulted the separation based on their low polarity and similarity of the products. To rationalize these likeness, the physicochemical properties were calculated *in silico* using the Molinspiration software.[26] As was expected, there are no substantial differences on the more relevant parameters of the isomers (log *P*, volume and TPSA), explaining the impossibility of the experimental products separation. As an example, in the case of the mixture **6b**: geranyl azide (**6b-*E***), neryl azide (**6b-*Z***) and linaloyl azide (**6b–t**) log *P* values, calculated as a lipophilicity parameter, were 4.54, 4.54 and 4.55, respectively. Those similarities, combined with the rapid interconversion at room temperature, made impossible to isolate any isomer.

Computational methods

The geometries of the reactants, the transition structures (TSs) and the products were optimized using MPWB1K[27] global hybrid *meta*-GGA functional together with 6-311++G(d,p) basis set. The MPWB1K has shown to be appropriate to obtain reliable geometries and for describing kinetics of organic reactions. Solvent effects in toluene (solvent used experimentally) were taken into account through full optimizations using the SMD continuum solvation method.[28] Frequency calculations were computed to verify the nature of the stationary points as true minima or as first order transition structure (TS) and to evaluate the thermal corrections. Free energies were calculated at 298.15 K and 1 atm in toluene. Intrinsic reaction coordinate (IRC) paths were traced using the Hessian-based predictor corrector (HPC)[29,30] algorithm to verify the connectivity of the TSs with reactants and products. All calculations were performed with the Gaussian 09 package.[31] The topological properties in the framework of the QTAIM theory were calculated using the AIMALL program.[32]

Equilibrium composition studies

Given the limited precedents of the equilibrium for this system, a complete study was necessary. These analyzes included the nature of the substrates (number of isoprene units and unsaturations), regiochemistry of the starting alcohol, solvent and temperature. The composition of each mixture at room temperature was determined by ^{1}H NMR spectra. First, a detailed analysis of the composition at the equilibrium of the mixture was carried out identifying the signals corresponding to

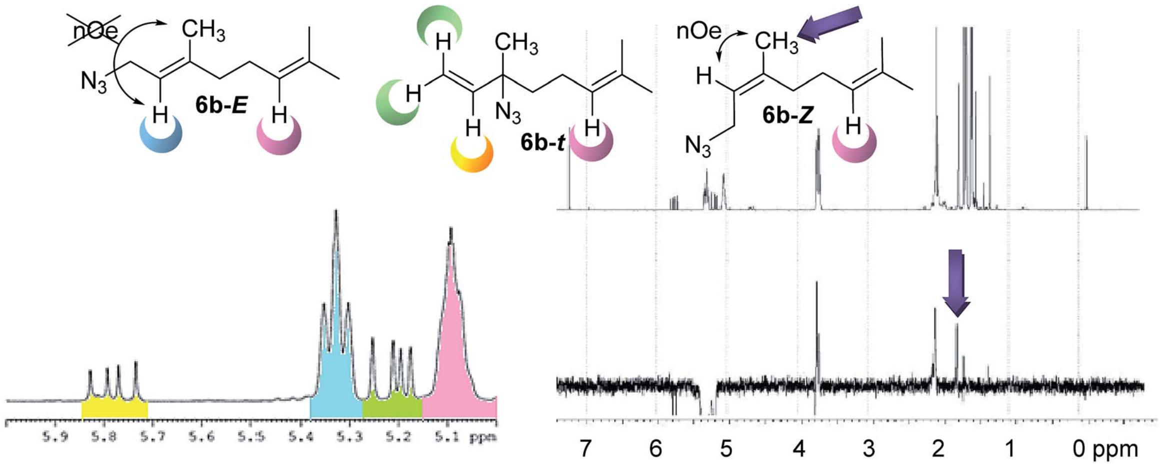
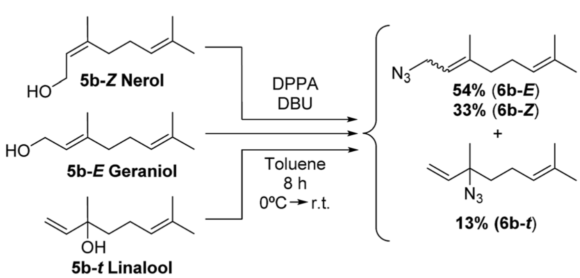


Fig. 3 Left: ^{1}H NMR spectrum of the double bond section of the mixture **6b**. Right: nOe experiment.

each component of the mixture. In the case of **6b** (**6b-*E***, **6b-*Z*** and **6b–t**) the solution ^{1}H NMR in $CDCl_3$ (Fig. 3), shows a multiplet at 5.09 ppm assignable to the common olefinic proton H-6 (pink) shared by all the isomers, being taken as a reference. A double doublet at 5.78 ppm is observed for the olefinic proton H-2 (yellow) of linaloyl azide **6b–t.** This azide is in a 13% in the mixture, as was expected, since it is the less substituted alkene. Finally, to calculate the *E* : *Z* ratio of the primary azides, nOe experiments selectively irradiating the triplet present at 5.33 ppm, which corresponds to the olefinic proton H-2 (blue) shown positive effect on the singlet present at 1.79 ppm. This signal is assigned to the methyl group of the *Z* isomer (**6b-*Z***), providing a ratio *E* : *Z* of 5 : 3.

The NMR analysis of the other mixtures (**6a**, **6c**, **6d** and **6e**) in $CDCl_3$ have shown that the azide composition remains constant regardless the number of isoprenyl units or (un)saturation grade, suggesting that increasing the number of isoprene units does not influence the equilibrium. It was noticed that primary allyl-azides are the major compounds present in the mixture (87%), while tertiary allyl-azides represent only 13% at room temperature. Concerning the composition of primary allyl-azides, the *E*- and *Z*-isomers correspond to 54% and 33% of the mixture, respectively.

To corroborate that the equilibrium composition is independent of the regiochemistry and the degree of substitution of the starting isoprenol, a set of reactions were conducted.



Scheme 2 Synthesis of the azide mixture from nerol, geraniol and linalool.

Independently, nerol (**5b-*Z***) and linalool (**5b–t**) were reacted under Thompson's conditions, providing the products with similar yield than that for geraniol (**5b-*E***). In those cases, a similar isomeric ratio was obtained regardless the precursor alcohol. Geranyl azide (**6b-*E***), neryl azide (**6b-*Z***), linalooyl azide (**6b–t**) were obtained in a 54 : 33 : 13 ratio, respectively (Scheme 2). Also, in different reported procedures to generate **6b** the same regioisomer proportions were obtained, regardless of reaction conditions used (temperature, solvents, reagents, catalysts).[16,21,33,34] These results demonstrate that isoprenyl azides cannot be obtained as pure isomer and consequently not requiring regiopure isoprenols for their preparation, which results in a significant cost reduction. The relative tertiary azide proportion increases 15% (Fig. 4, from 11.2% to 13.2%).

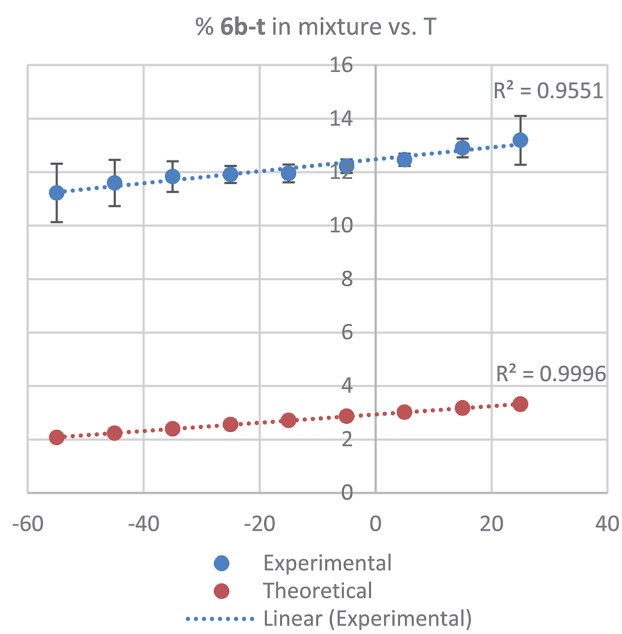


Fig. 4 Dependence of tertiary azide population *vs.* temperature (*T*) (blue = experimental, red = calculated).

Then, the temperature effect on the system was examined. NMR experiments were conducted in CD_2Cl_2 from −55 °C to 25 °C acquiring spectra every 10 °C. In that 80 degrees window, however, in the same experiment the primary regioisomer population composition change (**6b-*E*** and **6b-*Z***) is less appreciable (*E*-isomer increases only 7% at the same range of temperature, see ESI†). The same tendency was observed when the proportion of the tertiary azide on the equilibrium was analyzed theoretically (Fig. 4).

Strikingly, when the same experiment was conducted on DMSO-d_6 to increase the temperature beyond 80 °C, the integrity of the compound was affected based on the wide change on the ^{1}H NMR spectra. The decomposition of the azide was confirmed by the disappearance of the characteristic azide stretching band at 2200 to 2100 cm^{-1} in the IR spectrum. That unexpected reaction avoids expanding the equilibrium shift beyond that temperature.

The next step was to determine how the solvent polarity affects the equilibrium. 1% v/v solution of the **6b** in different deuterated solvents, including non-polar (benzene, toluene, chloroform), polar aprotic (THF, acetone, DCM, DMSO) and a protic solvent (MeOH). Those solvents cover a wide spectrum of dielectric constant (from 2.27 for benzene to 46.83 for DMSO). The analysis of the spectra revealed that the nature of solvents does not appreciably affect the azide population. The proportion of tertiary azide goes from 12.5% in chloroform to 13.7% in methanol, having a distribution between those values for the rest of the solvents. The theoretical calculations agree with the experimental results showing a small population difference among the solvents, demonstrating the low effect of the type of solvent on the population distribution.

It has previously been reported for other allyl azides systems that solvent exchange and temperature can be used to control the equilibrium composition. Thevenet *et al.* efficiently modulated the reactivity of allylazides controlling the [3,3]-sigmatropic rearrangement changing the solvent and the temperature of the reaction.[35] Our results showed that prenyl azides are insensitive to those changes, leaving equilibrium distribution solely dependent on the substrate structure.

Finally, to study how the structure affects the equilibrium, a set of new analogues were proposed. The methyl group should be exchange by a phenyl group (changing electronic and steric factors). Aromatic compounds containing isoprenyl substituents have interesting pharmacological profiles including antimicrobial, antifungal, anti-carcinogenic and anti-HIV activities.[36–38] The proposed phenyl derivatives **8** and **15**, inspired by prenyl azide mixtures **6a** were prepared. In both compounds one methyl group was replaced by an aromatic ring, keeping the other methyl group in one analog or being replace by a hydrogen (Fig. 5).

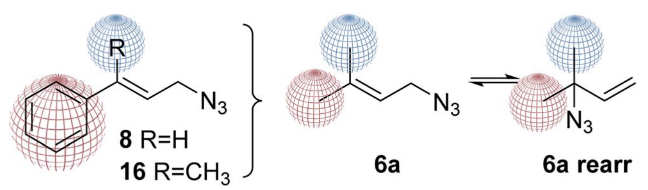
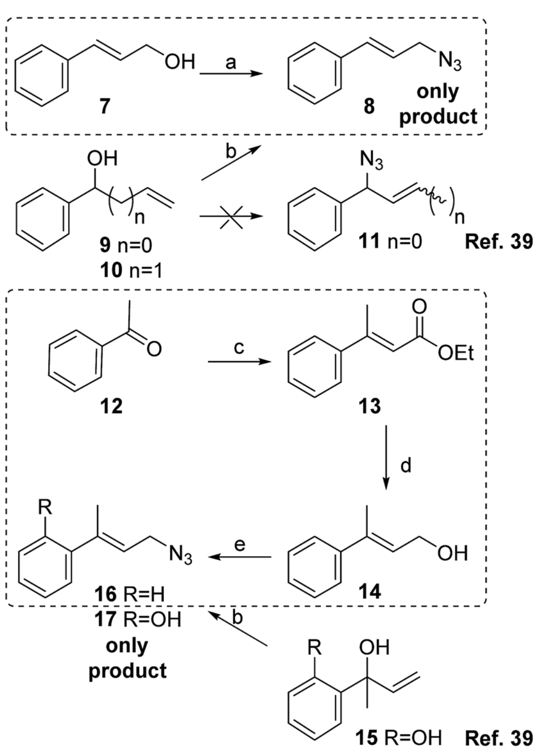


Fig. 5 Phenyl prenylazides proposed.

To prepare the phenyl substituted allylic azide **8**, cinnamyl alcohol **7** was transformed into the corresponding azide by Thompson's reaction with DPPA and DBU in toluene providing the expected product with 78% yield after purification (Scheme 3). Cinnamylazide **8** was obtained as the only product, maintaining the same regiochemistry of the starting material. This was confirmed by ^{1}H NMR visualization of the signal corresponding to the olefinic proton adjacent to the aromatic ring at 6.66 ppm with a $J = 15.8$ Hz, distinctive for the *E*-isomer. The other olefinic signal appears at 6.25 ppm as a double triplet ($J =$ 15.8 and 6.6 Hz).

Srinu *et al.* have obtained cinnamyl azide **8** from vinylbenzyl alcohol **9** using $BF_3 \cdot Et_2O$ and $TMSN_3$ without isolating the expected product **11**.[39] These authors proposed a S_N2' with the azide attacking the terminal olefinic carbon and releasing a TMSO as possible mechanism for that reaction. Different authors have also reported the same results using substituted phenyl propenols,[16,21,23,40] and different reagents and reaction conditions. The reaction of homoallylic alcohols using $TMSN_3$ under $PdCl_2$ catalysis also produced the conjugated products.[41]

In order to synthesize the isomeric mixture **16**, acetophenone **12** was submitted to a Horner–Wadsworth–Emmons reaction with triethylphosphonoacetate providing the α,β-



Scheme 3 Reagents and conditions: (a) DPPA, DBU, toluene, 12 h, 0 °C → rt, 78%; (b) $BF_3 \cdot Et_2O$, $TMSN_3$, DCM (ref. 39); (c) triethylphosphonoacetate, NaH, dimethoxyethane, 3 h, r.t., 60%; (d) $LiAlH_4$, THF, 1 h, rt, 80%; (d) DPPA, DBU, toluene, 12 h, 0 °C → r.t., 91%. In dotted lines, the synthetic routes developed in the present work.

unsaturated ester **13** in 3 hours with 60% yield ($E:Z$, 92 : 8, Scheme 3).

The ester was reduced with $LiAlH_4$ in THF in 1 hour, to get the alcohol **14** (80% yield). In this step, the E-isomer was separated by chromatography. Lastly, the alcohol was transformed into azide **16** by reaction with DPPA and DBU in toluene with 91% yield.

The ^1H NMR spectrum of product **16** shows a triplet at 5.88 ppm with a $J = 6.7$ Hz for the olefinic proton coupled with the protons of the allylic methylene of 3.99 ppm ($J = 6.7$ Hz). These signals are a clear indication that only one isomer has been formed without experiencing the [3,3]-sigmatropic rearrangement. Those results are also in agreement with the work reported by Srinu *et al.* where only the primary azide **16** was obtained starting from the alcohol **14** or an isomeric alcohol **15**[39] (Scheme 3).

In summary, our results and the literature precedents clearly showed that, in any case starting from conjugated allylic alcohols or their isomers phenethyl vinyl alcohols, only one conjugated product is obtained.

Products from the reactions with cinnamyl alcohol **7** and its methyl substituted derivative **14** retain their regiochemistry demonstrating that the presence of the aromatic ring disfavours the [3,3]-sigmatropic rearrangement due to stereoelectronic and inductive effects.

To rationalize the experimental evidences that showed a high dependency of the double bond substitution on the equilibrium of allylic alcohols, a theoretical study was performed. In contrast to the large number of experimental and theoretical investigations aimed to understand sigmatropic rearrangements of different systems,[35,42,43] azides has received scarce attention, especially from the theoretical point of view. In addition, an analysis based on the quantum theory of atoms in molecules (QTAIM)[44,45] was performed. Such studies provide information of the electron charge distribution involved in the [3,3]-sigmatropic rearrangements of **6a**, **8** and **12**. That approach is based on the topological analysis of the electron charge density allowing a clear insight into structure and the stability of a chemical species.

Theoretical studies of 6a, 8 and 16

Energetic, structural and electron charge density analysis. The free energy profiles for the [3,3]-sigmatropic rearrangement of **6a**, **8** and **12** showing the located stationary points with their corresponding relative free energies are displayed in Fig. 6. **TS-6a** ($\Delta G^{\#} = 26.0$ kcal mol^{-1}) has lower free activation energy than **TS-8** and **TS-16** (by 3.7 and 3.1 kcal mol^{-1}, respectively). The aromatic ring disfavours the stability of **TS-8** and **TS-16**, increasing the activation energies. The former is slightly less stable than the second one, which is attributed to the absence of methyl group. The [3,3]-sigmatropic rearrangement of **6a** is endergonic (ΔG = 1.8 kcal mol^{-1}) and the endothermicity increases for the aromatic systems **8** and **16** by 4.6 and 4.0 kcal mol^{-1}, respectively. Again, the presence of methyl group slightly favours the stability of the system.

Several topological properties evaluated at a bond critical point (bcp) are used to characterize the nature of a bonding interaction (calculated properties at the bcp are labelled with the subscript "b").

The charge density, ρ_b, reflects the bond strength and its Laplacian, $\nabla^2\rho_b$ gives information about the local charge concentration ($\nabla^2\rho_b < 0$) or depletion ($\nabla^2\rho_b > 0$).[44,45] The ellipticity, ε, provides information about the charge distribution around the bond path and can be used to determine the bond stability and its π character.[46] The total energy density, H_b, ($H_b = G_b + V_b$, being G_b and V_b the potential and the kinetic energy densities at the bcp, respectively), which designs the density of the total electronic energy at a bcp, is used to analyse the covalent character of an interaction.[47] Also, the delocalization index, DI, is an important parameter that indicates the amount of the electron pairs number shared by two atoms.[48,49]

The molecular graphs of the TSs under study are shown in Fig. 7 and the topological properties evaluated at the selected bcps are listed in Table 1 along with the bond distances (such properties for another bcps are given in the ESI†).

The molecular graphs of TSs show the bcps associated with forming C1–N1 and breaking C3–N3 bonds and a ring critical point (rcp) related to a half-chair cyclic structure.

In **TS-6a**, the values at the C1–N1 bcp of ρ_b (0.058 au.), $\nabla^2\rho_b$ (0.091 au.), and DI (0.32) are slightly lower than these calculated at the C3–N3 bcp ($\rho_b = 0.059$ au., $\nabla^2\rho_b = 0.095$ au., and DI = 0.37). In contrast, in **TS-8** and **TS-16**, the values of ρ_b and DI at C1–N1 bcp are slightly higher than these calculated at the C3–N3 bcp (except DI in **TS-16**, that in both bcps take the same value). Therefore, in TSs with aromatic ring substituent, the formation/rupture of C1–N1/C3–N3 bonds are more advanced than in TS with methyl substituents. These facts are also reflected toward the bond distances.

The topological properties evaluated at C1–C2 and C2–C3 bcps (see the ESI†) indicate that these bonds have an intermediate character between single and double covalent bond, due to the delocalization of the "π" electrons upon the C1–C2–C3 fragment. The double bond character is higher for the C2–C3 bond, being more notable in **TS-8** and **TS-16**.

The distances and topological properties of N1–N2 and N2–N3 bonds are quite similar, however, these show that the "π" electron density is slightly more localized on the N2–N3 bond particularly in **TS-8** and **TS-16**. The geometric and topological results support the existence of π-electron delocalization in the TSs and strongly suggest that the effect of the aromatic substituent is strictly electronic, thus the contribution of steric factor to the stability of the systems must be scarce or null.

In addition, an analysis of the variation of the topological properties at the selected bcps (C1–N1, C3–N3, C1–C2, C2–C3, N1–N2, N2–N3) along the reaction courses was carried out (see the ESI†). Such analysis has been successfully applied to rationalize the mechanism of a wide variety of chemical transformations.[46,50–58] The profiles of topological properties evaluated at the selected bcps showed similar patterns for all reaction pathways. The evolution of the topological properties of the pairs of bcps C1–N1 and C3–N3, C1–C2 and C2–C3, and N1–N2 and N2–N3, are complementary demonstrating that

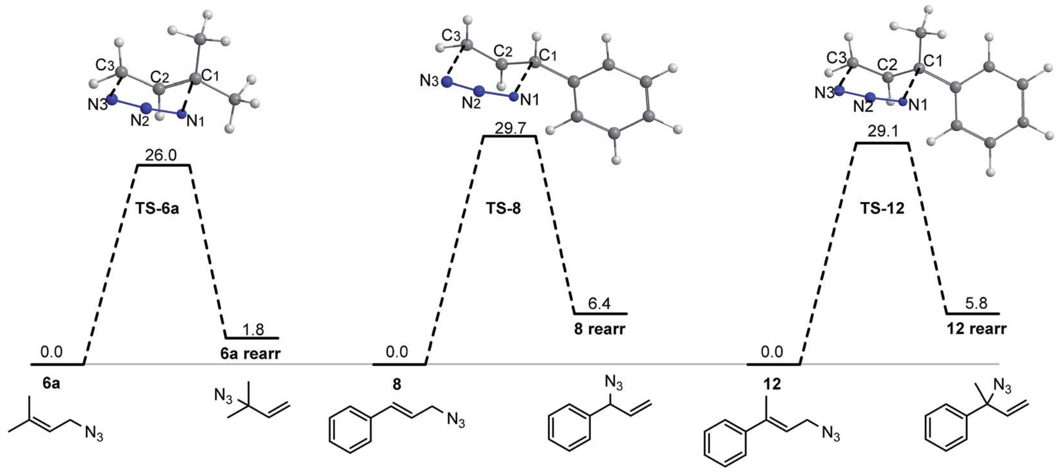


Fig. 6 MPWB1K/6-311++G(d,p) free energy profiles for the [3,3]-sigmatropic rearrangement of allylic azides **6a**, **8** and **16**. Relative free energies in toluene are in kcal mol^{-1}. The optimized geometries (in 3D) for the transition structures are showed.

a continuous electron transfer occurs. These results reinforce the fact that the effect of the aromatic substituent is strictly electronic.

Atomic properties analysis. The analysis of the changes in atomic populations $N(\Omega)$, and atomic energies $E(\Omega)$ is carried out to know the distribution of the electron charge density and to pinpoint the atoms or group of atoms that undergo the greatest changes in their atomic properties in achieving the TSs.[44,59–63]

Fig. 8 displays the changes in atomic population $\Delta N(\Omega)$ and atomic energy $\Delta E(\Omega)$ in the TSs respect to the corresponding reactants (**6a, 8** and **16**). The changes in such properties in the group of atoms, R1 and R2 that form the substituent fragments are also included. The net charges calculated for selected atoms in the TSs and azides **6a**, **8** and **16** are showed in Table 2.

The atoms in TSs whose atomic population and atomic energy were significantly affected respect to the reactant **6a**, **8** and **16** (*i.e.*, $|\Delta N(\Omega)| > 0.02\ e$, and $|\Delta E(\Omega)| > 20$ kcal mol^{-1}) are N1, N3 and C3. The C1 atom shows a considerable variation in its atomic energy, however, the change in its atomic population is less important. Thus, the largest changes of atomic properties to reach the TSs occur in the atoms involved in the forming and breaking bonds, particularly in the latter one.

The atomic properties of the remaining atoms and the group of atoms, R1 and R2, show relative lower changes in achieving the TSs. Overall, these atoms lose electron population and are

Table 1 Bond distances and topological properties for selected bcps calculated at the TSs under study[a,b]

Species	Bonds	R	ρ_b	$\nabla^2\rho_b$	ε	H_b	DI
TS-6a	C1–N1	2.14	0.058	0.091	0.142	−0.072	0.32
	C3–N3	2.11	0.059	0.095	0.104	−0.009	0.37
TS-8	C1–N1	2.08	0.063	0.092	0.133	−0.011	0.37
	C3–N3	2.15	0.054	0.096	0.120	−0.007	0.34
TS-16	C1–N1	2.13	0.059	0.089	0.138	−0.009	0.33
	C3–N3	2.17	0.052	0.095	0.123	−0.006	0.33

[a] Bond distances (R) in Å; ρ_b, $\nabla^2\rho_b$, H_b in au. ε and DI are dimensionless.
[b] To identify the atoms, see Fig. 7.

destabilized (except N2, which increases its electron population and is stabilized, and C2 in **TS-6a**, which decreases its atomic energy).

$N(\Omega)$ of C1 atom decrease taking its net charge values positive, +0.031, +0.022 and +0.027 e for **TS-6a**, **TS-8** and **TS-16**, respectively (Table 2). The destabilization of C1 increases in the order **TS-8** (19 kcal mol^{-1}) < **TS-6a** (25 kcal mol^{-1}) < **TS-16** (30 kcal mol^{-1}). The decrease of $N(\Omega)$ and the destabilization of C1 are related with the loss of "s" character.

Because of the C3–N3 bond is breaking, an increase of "s" over "p" character in C3 occurs and in consequence, it gains electron population. The largest amount of electron population

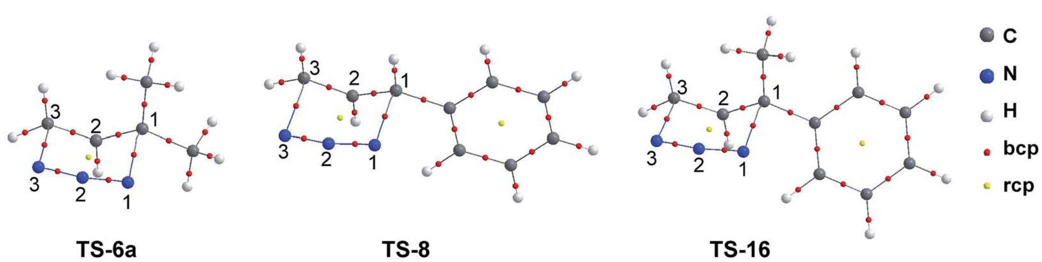


Fig. 7 Molecular graphs of the TSs corresponding to [3,3]-sigmatropic rearrangement of allylic azides **6a**, **8** and **12**.

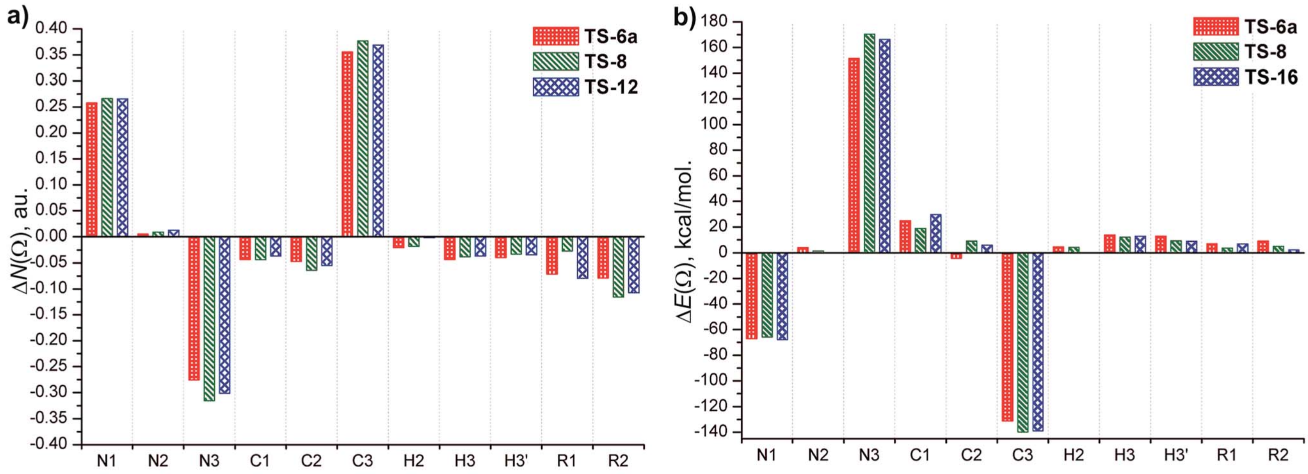


Fig. 8 Variation of (a) electron population, $\Delta N(\Omega)$, and (b) energy, $\Delta E(\Omega)$, for atoms and atom groups at the TSs with respect to the corresponding reactants. $\Delta N(\Omega) < 0$ and $\Delta N(\Omega) > 0$ indicate that the atom loses and gains electron population. $\Delta E(\Omega) < 0$ and $\Delta E(\Omega) > 0$ indicate that the atom is stabilized and destabilized at TS regarding to the corresponding reactants, respectively. R1 = Me, H, Me and R2 = Me, Ph, Ph in **TS-6a**, **TS-8** and **TS-16**, respectively. See Fig. 7 to identify atoms label.

gained by C3 comes mainly from all atoms of allylic fragment and R1 and R2 groups, which lose electron population. The π-electrons of aromatic substituent in **TS-8** and **TS-16** may be better delocalized than the electrons donated by the methyl group in **TS-6a**, and the electron transfer toward C3 may occur due to the delocalization of the charge density of the double bond C1–C2. Consequently, the C3 atom in **TS-8** (0.37 *e*) and **TS-16** (0.36 *e*) gains a slightly greater electron population than in **TS-6a** (0.35 *e*), and it is more stabilized in the former TSs (ΔE(C3) = −140 and −138 kcal mol^{-1} for **TS-8** and **TS-16**, and −131 kcal mol^{-1} for **TS-6a**). In addition, a good linear correlation between ΔN(C3), ΔE(C3) and $\Delta G^{\#}$(R^2 = 0.891 and 0.995, respectively) is obtained (see the ESI†). Thus, ΔN(C3) reflects the effect of the different substituents upon the electron delocalization but the stabilization of C3 is inverse to the values of $\Delta G^{\#}$, and therefore does not explain the high energy barriers.

The loss of electron population of N3 increases in the order **TS-6a** (−0.27 *e*) > **TS-16** (−0.30 *e*) > **TS-8** (−0.31 *e*), and its net charge becomes less negative (Table 2) due to the partial breaking of C3–N3 bond. This trend is contrary to the increase of electron population of C3, and reflects the effect of the substituents. In addition, a good linear correlation between ΔN(N3) and $\Delta G^{\#}$ (R^2 = 0.921), is obtained (see the ESI†). N3 is destabilized due to the loss of a great amount of electron population in achieving the TSs. The increase of ΔE(N3) follows the order **TS-16** (170 kcal mol^{-1}) > **TS-8** (166 kcal mol^{-1}) > **TS-6a** (151 kcal mol^{-1}), which is in line with the increase of free activation energy calculated. Accordingly, a strong linear dependence of ΔE(N3) on $\Delta G^{\#}$ is established (R^2 = 0.994, see the ESI†). These results clearly demonstrate that the relatively high free activation energy for the [3,3]-sigmatropic rearrangement under study come from the great destabilization of N3.

Table 2 Atomic net charges (in e) for selected atoms in the azides **6a**, **8** and **12** and the in TSs under study

Species	q(C1)	q(C2)	q(C3)	q(N1)	q(N2)	q(N3)
6a	−0.012	−0.035	+0.352	+0.124	−0.213	−0.402
TS-6a	+0.031	+0.012	−0.004	−0.134	−0.219	−0.127
8	−0.022	−0.045	+0.374	0.138	−0.211	−0.420
TS-8	+0.022	+0.019	−0.003	−0.129	−0.220	−0.105
16	−0.010	−0.038	+0.359	+0.136	−0.213	−0.414
TS-16	+0.027	+0.017	−0.010	−0.131	−0.226	−0.112

In a related reaction, the Cope rearrangement of 1,5-hexadiene, the great destabilization of two ethylenic terminal carbons (C1 and C6) was considered as the "source" of the high barrier for this reaction. In the case of the sigmatropic rearrangement of isoprenylazides, the particular redistribution of the electron charge density which makes the destabilization of N3, is attributed to the singular electronic characteristic of the azide group.

The charge loss by N3 achieving the TSs is mainly transferred to N1, which increased its electron and is stabilized, but less than C3. The stabilization of the N1 and C3 atoms in the TSs contributes to lowering the energy barrier although the destabilization of N3 is more relevant.

Additionally, an analysis of the evolution of $\Delta N(\Omega)$ and $\Delta E(\Omega)$ along the course of reaction was performed (see the ESI†). Such analysis demonstrates that the atomic properties of C1, C3, N1 and N3 are significantly affected along the reaction pathways. Interestingly, the profiles of ΔE(N3) have a similar pattern but show larger differences in quantitative sense which is in agreement with the energy barriers of the reaction under study.

Conclusions

Since the advent of click chemistry, azides play a key role in the synthesis of 1,2,3-triazoles. Isoprenyl azides can be considered an important synthetic intermediate to generate new chemotherapeutic entities. Their use has been disfavoured since they tend to produce Winstein's rearrangements, producing a mixture of chromatographically inseparable regioisomers.

In this work, isoprenylic azides were synthesized, using NMR spectroscopy to identify the regioisomers' ratio. It was observed that the ratio remains unchanged at room temperature regardless the number of isoprene units, regiochemistry and the substitution of the starting isoprenol. Additionally, when isoprene double bond was decorated with aromatic rings, the azide do not experiment the [3,3]-sigmatropic rearrangement. The equilibrium composition dependence with the temperature and the solvent were also analysed. From −55 to 25 °C, the tertiary azide proportion increases only 15% (11.2% to 13.2%). The study curry out on eight different solvents showed that the equilibrium is not appreciably affected. Those results were confirmed by theoretical calculation where the energy difference for the isomers on different solvents has low impact on the equilibrium population distribution. Together, those results proved that isoprenyl azides cannot be experimentally obtained as pure isomer.

To rationalize the experimental results, theoretical studies were performed using density functional theory and the QTAIM approach. The free energy barrier and the endothermicity of the reaction involving aromatic azides were higher than that of methyl azides. Thus, Winstein' rearrangement of aromatic systems is kinetically and thermodynamically disfavoured which is in agreement with the experimental results. The topological analysis of the electron charge density revealed that the rearrangement takes place *via* a concerted mechanism involving a half-chair TS in which a significant redistribution of the charge density occurs. Additionally, it was demonstrated that the effect of the aromatic substituent is purely electronic.

The analysis of atomic properties allowed pinpoint the atoms or region that experience the greatest changes in electron population and energy in achieving the TSs. Although the effect of the substituent affects the properties of the whole systems, it was found that the destabilization of N3 plays a key role in the larger energy barrier, and clearly reflects the degree of electron delocalization caused by the substituent effect.

Therefore, the formation of the tertiary regioisomers through [3,3]-sigmatropic rearrangement may be controlled by modifying the electronic structure of isoprenylazides.

Experimental

General information

^{1}H and ^{13}C NMR spectra were acquired on a BrukerAvance II 300 MHz (75.13 MHz) using $CDCl_3$ as solvent. Chemical shifts (δ) were reported in ppm downfield from tetramethylsilane (TMS) at 0 ppm as internal standard and coupling constants (J) are in hertz (Hz). Chemical shifts for carbon nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million relative to the center line of the $CDCl_3$ triplet at 76.9 ppm. The following abbreviations are used to indicate NMR signal multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentuplet, m = multiplet, br = broad signal. Electrospray and Atmospheric Pressure Chemical Ionization High-resolution mass spectra (ESI-HRMS, APCI-HRMS) were recorded on a BrukerMicroTOF II with lock spray source. IR spectra were obtained using an FTIR Shimadzu spectrometer and only partial spectral data are listed. Chemical reagents were purchased from commercial suppliers and used without further purification, unless otherwise noted. Solvents were analytical grade or were purified by standard procedures prior to use. Yields were calculated for material judged homogeneous by thin layer chromatography (TLC) and nuclear magnetic resonance (^{1}H-NMR). All reactions were monitored by thin layer chromatography performed on silica gel 60 F_{254} pre-coated aluminum sheets, visualized by a 254 nm UV lamp, and stained with an ethanolic solution of 4-anisaldehyde. Column flash chromatography was performed using silica gel 60 (230–400 mesh).

General procedure for prenyl azides synthesis

One equivalent of the prenyl alcohol substrate was dissolved in anhydrous toluene at 0 °C. Then, 1.3 equivalents of diphenylphosphorylazide (DPPA) were added followed by the addition of 1.3 equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). After 2 h of continuous stirring at 0 °C, the reaction was warmed to room temperature. Finally, the mixture of reaction was quenched with water. The aqueous layer was extracted 3 times with ethyl acetate and the combined organic layers concentrated under vacuum. The residue was purified on a silica gel column (hexane).

Synthesis of mixture of allylazides from the prenol: 1-azido-3-methylbut-2-ene (6a) and 3-azido-3-methylbut-1-ene (6a rearr). Following the general reaction conditions for the prenyl azides synthesis, 3-methylbut-2-en-1-ol **5a** (100 mg; 1.16 mmol) was dissolved in anhydrous toluene (2.5 mL). Then, DPPA was slowly added (400 mg, 1.51 mmol) followed by the addition of DBU (232 mg; 1.51 mmol). After 8 h of continuous stirring at room temperature, the reaction was worked up and purified to afford 108 mg of the product as a colourless oil (isolated yield: 84%).^{1}H NMR ($CDCl_3$): δ 5.94 ppm (dd, 0.16H, $^3J_{H2-H1} = 17.3$ Hz and $^3J_{H2-H1} = 10.7$ Hz, C2$_t$–H); 5.41 (tt, 1H, $^3J_{H2-H1} = 7.5$ Hz and $^4J_{H2-H4} = 1.4$ Hz, C2$_P$–H); 5.31 (d, 0.16H, $^3J_{H1-H2} = 17.3$ Hz, C1$_T$–H); 5.24 (d, 0.16H, $^3J_{H1-H2} = 10.7$ Hz, C1$_T$–H); 3.83 (d, 2.06H,$^3J_{H1-H2} = 7.3$ Hz, C1$_P$–H); 1.89 (s, 3.15H, C5$_P$–H); 1.79 (s, 3.15H, C4$_P$–H) and 1.43 (s, 1.15H, C4$_T$–H and C5$_T$–H). ^{13}C NMR ($CDCl_3$): δ 141.2 ppm (C$_T$2, CH); 139.6 (C$_P$3, quaternary); 117.4 (C$_P$2, CH); 113.9 (C$_T$1, CH_2); 49.6 (C$_T$3, quaternary); 48.2 (C$_P$1, CH_2); 26.1 (C$_T$4 and C$_T$5, CH_3); 25.7 (C$_P$4, CH_3) and 18.1 (C$_P$5, CH_3).

Synthesis of mixture of allyl azides from the geraniol: (*E*)-1-azido-3,7-dimethylocta-2,6-diene (6b-*E*); (*Z*)-1-azido-3,7-dimethylocta-2,6-diene (6b-*Z*) and 3-azido-3,7-dimethylocta-1,6-diene (6b–t). Following the general reaction conditions for the prenyl azides synthesis, geraniol **5b-*E*** (600 mg; 3.90 mmol) was dissolved in anhydrous toluene (8 mL). Then, DPPA was slowly added (1320 mg, 5.00 mmol) followed by the addition of DBU (770 mg; 5.00 mmol). After 8 h of continuous stirring at room temperature, the reaction was worked up and purified to afford 608 mg of colourless oil (isolated yield: 87%).^{1}H NMR

($CDCl_3$): δ 5.78 ppm (dd, 0.12H, $^3J_{H2-H1\ trans}$ = 17.3 Hz and $^3J_{H2-H1\ cis}$ = 10.7 Hz, $C2_T$–H); 5.33 (t, 0.88H, $^3J_{H2-H1}$ = 7.3 Hz, $C2_E$–H and $C2_Z$–H); 5.23 (d, 0.14H, $^3J_{H1\ trans-H2}$ = 17.3 Hz, $C1_T$–H); 5.20 (d, 0.14H, $^3J_{H1\ trans-H2}$ = 10.7 Hz, $C1_T$–H); 5.09 (m, 1H, C7–H); 3.75 (dd, 1.85H, $^3J_{H1-H2}$ = 7.2 Hz, $C1_E$–H and $C1_Z$–H); 2.10 (bs, 3.67H, C5–H and C6–H); 1.79 (s, 1.07H, $C4_Z$–H); 1.70 (s, 1.87H, $C4_E$–H); 1.68 (s, 3H, C10–H), 1.61 (s, 3H, C9–H) and 1.35 (s, 0.41H, $C4_T$–H). ^{13}C NMR ($CDCl_3$): δ 143.1 ppm (C_E3, quaternary); 143.0 (C_Z3, quaternary); 140.1 (C_T2, quaternary); 132.3 (C_Z8, quaternary); 132.1 (C_T8, quaternary); 131.9 (C_E8, quaternary); 123.6 (C_E7, CH); 123.5 (C_T7, CH); 123.4 (C_Z7, CH); 117.9 (C_Z2, CH); 117.0 (C_E2, CH); 114.6 (C_T1, CH_2); 64.9 (C_T3, quaternary); 48.0 (C_E1, CH_2); 47.9 (C_Z1, CH_2); 40.1 (C_T5, CH_2); 39.5 (C_E5, CH_2); 32.1 (C_Z5, CH_2); 26.7 (C_Z6, CH_2); 26.4 (C_E6, CH_2); 25.6 (C_Z10, C_E10, CH_3); 23.3 (C_Z4, CH_3); 23.1 (C_T4, CH_3); 22.8 (C_T6, CH_2); 17.7 (C_T9, CH_3); 17.6 (C_E9, CH_3); 17.6 (C_Z9, CH_3) and 16.4 (C_E4, CH_3). HRMS (APCI): calculated mass for $C_{10}H_{18}N^-$ 152.14447; found 152.14438. IR (film): υ_{max} (cm^{-1}) 2969 (=CH–), 2928 (–CH_2–), 2884 (–CH_2–C–N–), 2098 (–N_3), 1664 (–C=C–).

Synthesis of mixture of allylazides from the nerol: (*E*)-1-azido-3,7-dimethylocta-2,6-diene (6b-*E*); (*Z*)-1-azido-3,7-dimethylocta-2,6-diene (6b-*Z*) and 3-azido-3,7-dimethylocta-1,6-diene (6b–t). Following the general reaction conditions for the prenylazides synthesis, nerol **5b-*Z*** (100 mg; 0.65 mmol) was dissolved in anhydrous toluene (2 mL). Then, DPPA was slowly added (220 mg, 0.83 mmol) followed by the addition of DBU (129 mg; 0.83 mmol). After 8 h of continuous stirring at room temperature, the reaction was worked up and purified to afford 104 mg of colourless oil (isolated yield: 89%). The spectra of ^{1}H and ^{13}C coincident with spectra obtained of mixture of allylic azides from the geraniol.

Synthesis of mixture of allyl azides from the linalool: (*E*)-1-azido-3,7-dimethylocta-2,6-diene (6b-*E*); (*Z*)-1-azido-3,7-dimethylocta-2,6-diene (6b-*Z*) and 3-azido-3,7-dimethylocta-1,6-diene (6b–t). Following the general reaction conditions for the prenyl azides synthesis, linalool **5b–t** (100 mg; 0.65 mmol) was dissolved in anhydrous toluene (2 mL). Then, DPPA was slowly added (220 mg, 0.83 mmol) followed by the addition of DBU (129 mg; 0.83 mmol). After 8 h of continuous stirring at room temperature, the reaction was worked up and purified to afford 99 mg of colourless oil (isolated yield: 85%).

The spectra of ^{1}H and ^{13}C coincide with spectra obtained of mixture of allylic azides from the geraniol.

Synthesis of mixture of allylazides from the farnesol: (2*E*,6*E*)-1-azido-3,7,11-trimethyldodeca-2,6,10-triene (6c-*E*); (2*Z*,6*E*)-1-azido-3,7,11-trimethyldodeca-2,6,10-triene (6c-*Z*) and (*E*)-3-azido-3,7,11-trimethyldodeca-1,6,10-triene (6c–t). Following the general reaction conditions for the prenylazides synthesis, farnesol **5c** (300 mg; 1.35 mmol) was dissolved in anhydrous toluene (4 mL). Then, DPPA was slowly added (355 mg, 1.75 mmol) followed by the addition of DBU (270 mg; 1.75 mmol). After 8 h of continuous stirring at room temperature, the reaction was worked up and purified to afford 284 mg of colourless oil (isolated yield: 85%). ^{1}H NMR ($CDCl_3$): δ 5.79 ppm (dd, 0.12H, $^3J_{H2-H1\ trans}$ = 17.3 Hz and $^3J_{H2-H1\ cis}$ = 10.7 Hz, $C2_T$–H); 5.34 (t, 0.87H, $^3J_{H2-H1}$ = 7.3 Hz, $C2_E$–H and $C2_Z$–H); 5.24 (d, 0.12H, $^3J_{H1\ trans-H2}$ = 17.3 Hz, $C1_T$–H); 5.21 (d, 0.12H, $^3J_{H1-H2}$ = 10.7 Hz, $C1_T$–H); 5.09 (m, 2H, C7–H and C12–H); 3.77 (d, 1.77H, $^3J_{H1-H2}$ = 7.3 Hz, $C1_E$–H and $C1_Z$–H); 2.11 (m, 8H, C5–H, C6–H, C10–H, C11–H); 1.80 (s, 1.05H, $C4_Z$–H); 1.71 (s, 2.01H, $C4_E$–H); 1.68 (s, 3H, C15–H); 1.61 (s, 6H, C9–H and C14–H); 1.55 (s, 0.40H, $C9_T$–H) and 1.35 (s, 0.40H, $C4_T$–H). ^{13}C NMR ($CDCl_3$): δ 143.1 (C_E3, quaternary); 143.0 (C_Z3, quaternary); 140.1 (C_T2, CH); 135.9 (C_Z8, quaternary); 135.7 (C_T8, quaternary); 135.6 (C_E8, quaternary); 131.3 and 131.2 (C_E13, C_Z13 and C_T13, quaternary); 124.3 (C_E12, C_Z12 and C_T12, CH); 123.5 (C_E7, CH); 123.4 (C_T7, CH); 123.3 (C_Z7, CH); 117.9 (C_Z2, CH); 117.1 (C_E2, CH); 114.6 (C_T1, CH_2); 64.9 (C_T3, quaternary); 48.0 (C_E1 and C_Z1, CH_2); 40.1 (C_T5, CH_2); 39.7 (C_T10, CH_2); 39.5 (C_E5, CH_2); 32.1 (C_Z5, CH_2); 26.7 (C_E6, C_Z6, C_Z10, C_E10, CH_2); 25.6 (C14, CH_3); 23.3 (C_T4, CH_3); 23.1 (C_E4, CH_3); 22.7 (C_T6, CH_2); 17.6 (C15, CH_3); 16.4 (C_E4, CH_3); 16.0 (C9, CH_3) and 15.9 (C_Z4, CH_3). HRMS (APCI): mass calculated for $C_{15}H_{26}N^-$ 220.20707, found 220.21291. IR (film): υ_{max} (cm^{-1}) 2968 (=CH–), 2926 (–CH_2–), 2856 (–CH_2–C–N–), 2097 (–N_3), 1665 (–C=C–).

Synthesis of mixture of allylazides from the geranylgeraniol: (2*E*,6*E*,10*E*)-1-azido-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraene (6d-*E*); (2*Z*,6*E*,10*E*)-1-azido-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraene (6d-*Z*) and (6*E*,10*E*)-3-azido-3,7,11,15-tetramethylhexadeca-1,6,10,14-tetraene (6d–t). Following the general reaction conditions for the prenylazides synthesis, geranylgeraniol **5d** (50 mg; 0.17 mmol) was dissolved in anhydrous toluene (1 mL). Then, DPPA was slowly added (58 mg, 0.22 mmol) followed by the addition of DBU (34 mg; 0.22 mmol). After 8 h of continuous stirring at room temperature, the reaction was worked up and purified to afford 49 mg of colorless oil (isolated yield: 92%). ^{1}H NMR ($CDCl_3$): δ 5.79 ppm (dd, 0.12H, $^3J_{H2-H1\ trans}$ = 17.3 Hz and $^3J_{H2-H1\ cis}$ = 10.7 Hz, $C2_T$–H); 5.34 (t, 0.93H, $^3J_{H2-H1}$ = 7.3 Hz, $C2_E$–H and $C2_Z$–H); 5.23 (d, 0.14H, $^3J_{H1\ trans-H2}$ = 17.3 Hz, $C1_T$–H); 5.20 (d, 0.14H, $^3J_{H1-H2}$ = 10.7 Hz, $C1_T$–H); 5.10 (m, 3H, C7–H, C12–H and C17–H); 3.78 (d, 1.78H, $^3J_{H1-H2}$ = 7.3 Hz, $C1_E$–H); 3.76 (d, 1.78H, $^3J_{H1-H2}$ = 7.3 Hz, $C1_Z$–H); 2.05 (m, 12H, C5–H, C6–H, C10–H, C11–H, C15–H and C16–H); 1.80 (s, 1.07H, $C4_Z$–H); 1.71 (s, 3H, $C4_E$–H); 1.68 (s, 3H, C15–H); 1.61 (s, 9H, C9–H, C14–H and C19–H); 1.55 (s, 3H, C20–H) and 1.35 (s, 0.45H, $C4_T$–H). ^{13}C NMR ($CDCl_3$): δ 143.2 ppm (C_E3, quaternary); 143.1 (C_Z3, quaternary); 140.1 (C_T2, quaternary); 136.0 (C_Z8, quaternary and C_T8, quaternary); 135.6 (C_E8, quaternary); 135.0 (C13, quaternary); 131.3 (C18, quaternary); 124.4 (C17, CH); 124.2 (C_Z12, CH); 124.2 (C_T12, CH); 124.1 (C_E12, CH); 123.5 (C_E7, CH); 123.5 (C_T7, CH); 123.3 (C_Z7, CH); 117.9 (C_Z2, CH); 117.0 (C_E2, CH); 117.0 (C_T1, CH_2); 64.9 (C_T3, quaternary); 48.1 (C_E1, CH_2); 48.0 (C_Z1, CH_2); 40.1 (C_T5, CH_2); 39.7 (C11, CH_2); 39.7 (C16, CH_2); 39.5 (C_E5, CH_2); 32.1 (C_Z5, CH_2); 26.8 (C16, CH_2); 26.6 (C10, CH_2); 26.4 (C_E6 and C_Z6, CH_2); 25.7 (C20, CH_3); 23.4 (C_E4, CH_3); 23.2 (C_T4, CH_3); 22.7 (C_T6, CH_2); 17.7 (C19, CH_3); 16.4 (C14, CH_3); 16.0 (C_Z4, CH_3) and 16.0 (C9, CH_3). IR (film): υ_{max} (cm^{-1}) 2967 (=CH–), 2928 (–CH_2–), 2882 (–CH_2–C–N–), 2096 (–N_3), 1660 (–C=C–).

Synthesis of mixture of allylazides from the phytol: (*E*)-1-azido-3,7,11,15-tetramethylhexadec-2-ene (6e-*E*); (*Z*)-1-azido-3,7,11,15-tetramethylhexadec-2-ene (6e-*Z*) and (3R)-3-azido-3,7,11,15-tetramethylhexadec-1-ene (6e–t). Following the general reaction conditions for the prenylazides synthesis, phytol **5e** (300 mg; 1.01 mmol) was dissolved in anhydrous toluene (4 mL). Then, DPPA was slowly added (270 mg, 1.33 mmol) followed by the addition of DBU (205 mg; 1.33 mmol). After 8 h of continuous stirring at room temperature, the reaction was worked up and purified to afford 282 mg of colourless oil (isolated yield: 87%). ^{1}H NMR ($CDCl_3$): δ 5.78 ppm (dd, 0.13H, $^3J_{H2-H1\ trans} = 17.3$ Hz and $^3J_{H2-H1\ cis} = 10.7$ Hz, $C2_T$–H); 5.34 (tq, 0.92H, $^3J_{H2-H1} = 7.5$ Hz, $C2_E$–H and $C2_Z$–H); 5.24 (dd, 0.12H, $^3J_{H1\ trans-H2} = 17.3$ Hz, $C1_T$–H); 5.19 (d, 0.12H, $^3J_{H1-H2} = 10.7$ Hz, $C1_T$–H); 3.78 (d, 1.93H, $^3J_{H1-H2} = 7.3$ Hz, $C1_E$–H and $C1_Z$–H); 2.05 (m, 2H, $C5_E$–H and $C5_Z$–H); 1.78 (s, 3H, $C4_Z$–H); 1.70 (s, 3H, $C4_E$–H); 1.54 to 1.15 (m, 19H, CH_2 and CH) and 0.88 to 0.83 (m, 12H, CH_3). ^{13}C NMR ($CDCl_3$): δ 143.7 ppm (C_E3 and C_Z3, quaternary); 140.3 (C_T2, quaternary); 117.5 (C_Z2, CH); 116.8 (C_E2, CH); 114.5 (C_T1, CH_2); 65.2 (C_T3, quaternary); 48.1 (C_E1, CH_2); 47.9 (C_Z1, CH_2); 40.5 (C_T5, CH_2); 39.5 (C_E5, CH_2); 39.4 (C17, CH_2); 28.0 (C18; CH) and 16.4 (C_E4, CH_3).

Synthesis of (*E*)-(3-azidoprop-1-en-1-yl) benzene (8). Following the general reaction conditions for the prenylazides synthesis, cinnamyl alcohol 7 (50 mg; 0.37 mmol) was dissolved in anhydrous toluene (2 mL). Then, DPPA was slowly added (126 mg, 0.48 mmol) followed by the addition of DBU (74 mg; 0.48 mmol). After 8 h of continuous stirring at room temperature, the reaction was worked up and purified to afford 47 mg of colorless oil (isolated yield: 78%). ^{1}H NMR ($CDCl_3$): δ 7.36 ppm (m, 5H, aromatics); 6.67 (bd, 1H, $^3J_{H7-H8\ trans} = 15.8$ Hz, C7–H); 6.27 (dt, 1H, $^3J_{H8-H7\ trans} = 15.7$ Hz, $^3J_{H8-H9} = 6.6$ Hz, C8–H) and 3.96 (bd; 2H, $^3J_{H9-H8} = 6.5$ Hz, C9–H). ^{13}C NMR ($CDCl_3$): δ 136.1 (C1, *ipso* aromatic); 134.6 (C7, quaternary olefinic); 128.7 (C3 and C5, *meta* aromatics); 128.2 (C4, *para* aromatic); 126.7 (C2 and C6, *ortho* aromatics); 122.5 (C8, CH olefinic) and 53.0 (C9, N–CH_2–).

Synthesis of (*E*)-ethyl 3-phenylbut-2-enoate (13*E*). 1.1 equivalents of sodium hydride (55.2 mg, 2.3 mmol) were dissolved in 4 mL of anhydrous dimethoxy ethane at room temperature and inert atmosphere. Then, 1.1 equivalents of triethylphosphonoacetate (TEPA, 517 mg, 2.3 mmol) were added followed by the slowly addition of 1 equivalent of acetophenone (250 mg, 2.1 mmol). After 3 h of continuous stirring, the reaction was quenched with water. The inorganic phase was extracted 3 times (3 × 30 mL) with ethyl ether and the combined organic layers concentrated under vacuum. The residue was purified on a silica gel column (hexane : ethyl acetate) to afford 205 mg of colourless oil (isolated yield: 60%, ratio *E*/*Z* 92 : 8). ^{1}H NMR ($CDCl_3$): δ 7.47 ppm (m, 2H, *meta* aromatics, C3–H and C5–H); 7.37 (m, 3H, *ortho* and *para* aromatics, C2–H, C4–H and C6–H); 6.14 (dd, 1H, olefinic, C8–H, $^4J_{H8-H10} = 1.3$ Hz); 4.22 (q, 2H, $^3J_{H11-H12} = 7.1$ Hz, C11–H); 2.58 (d, 3H, $^4J_{H10-H8} = 1.2$ Hz, C10–H) and 1.32 (t, 3H, $^3J_{H12-H11} = 7.1$ Hz, C12–H). ^{13}C NMR ($CDCl_3$): δ 166.9 (C9, carbonyl); 155.5 (C7, quaternary olefinic); 142.3 (C1, *ipso* aromatic); 129.0 (C4, *para* aromatic); 128.5 (C3 and C5, *meta* aromatics); 126.3 (C2 and C6, *ortho* aromatics); 117.2 (C8, CH, olefinic); 59.8 (C11, O–CH_2–); 17.9 (C10, CH_3) and 14.3 (C12, CH_3). HRMS: mass calculated for $C_{12}H_{15}O_2^+$ (M + H$^+$), 191.10666; found, 191.10670. IR (film): υ_{max} (cm^{-1}) 2978 (=CH–), 2926 (–CH2–), 1713 (C=O), 1628 (C=C).

(*Z*)-Ethyl 3-phenylbut-2-enoate (13*Z*). ^{1}HNMR ($CDCl_3$): δ 7.47 ppm (m, 2H, *meta* aromatics, C3–H and C5–H); 7.37 (m, 3H, *ortho* and *para* aromatics, C2–H, C4–H and C6–H); 5.91 (dd, 1H, olefinic, C8–H); 4.00 (q, 2H, $^3J_{H11-H12} = 7.1$ Hz, C11–H); 2.18 (d, 3H, $^4J_{H10-H8} = 1.2$ Hz, C10–H) and 1.08 (t, 3H, $^3J_{H12-H11} = 7.1$ Hz, C12–H). ^{13}C NMR ($CDCl_3$): δ 166.9 ppm (C9, carbonyl); 155.3 (C7, quaternary olefinic); 142.3 (C1, *ipso* aromatic); 128.0 (C3 and C5, *meta* aromatics); 127.8 (C4, *para* aromatic); 126.9 (C2 and C6, *ortho* aromatic); 117.9 (C8, CH, olefinic); 59.8 (C11, O–CH_2–); 29.6 (C10, CH_3) and 14.3 (C12, CH_3). HRMS (ESI): calculated mass for $C_{12}H_{15}O_2^+$ (M + H$^+$), 191.10666; found, 191.10670. IR (film): υ_{max} (cm^{-1}) 2978 (=CH–), 2926 (–CH_2–), 1713 (C=O), 1628 (C=C).

Synthesis of (*E*)-3-phenylbut-2-en-1-ol (14). 1 equivalent of compound **10** (50 mg, 0.21 mmol) was dissolved in 2 mL of anhydrous tetrahydrofuran at room temperature and inert atmosphere. Then, 2.5 equivalents of $LiAlH_4$ (20 mg, 0.50 mmol) were slowly added. After 1 h of vigorous stirring, the reaction was quenched with a mixture methanol : water (90 : 10), followed by the addition of 5 mL of a NH_4Cl solution (10% w/w). A partial evaporation of the mixture is performed to remove interfering solvent. The inorganic phase was extracted 3 times (3 × 15 mL) with ethyl ether and the combined organic layers concentrated under vacuum. The residue was purified on a silica gel column (hexane : ethyl acetate) to afford 34 mg of colourless oil (isolated yield: 80%). ^{1}H NMR ($CDCl_3$): δ 7.42 ppm (m, 2H, *meta* aromatic, C3–H and C5–H); 7.37 (t, 2H, *ortho* aromatics, C2–H and C6–H); 7.21 (d, 1H, *para* aromatic, C4–H); 5.98 (dt, 1H, $^3J_{H8-H9} = 6.7$ Hz, $^4J_{H8-H10\ trans} = 1.3$ Hz, C8–H); 4.37 (q, 2H, $^3J_{H9-H8} = 6.7$ Hz, C9–H) and 2.09 (d, 3H, $^4J_{H10-H8} = 1.3$ Hz, C10–H). ^{13}C NMR ($CDCl_3$): δ 142.9 ppm (C1, *ipso* aromatic); 128.5 (C7, quaternary olefinic); 128.3 (C3 and C5, *meta* aromatics); 127.0 (C4, *para* aromatic); 125.8 (C2 and C6, *ortho* aromatics); 60.0 (C9, O–CH_2–) and 16.0 (C10, CH_3). HRMS (ESI): mass calculated for $C_{10}H_{13}O^+$ (M + H$^+$), 149.09609; found, 149.09610. IR (film): υ_{max} (cm^{-1}) = 3402 (O–H), 2969 (=CH–), 2921 (–CH_2–).

Synthesis of (*E*)-(4-azido-but-2-en-2-yl) benzene (16). Following the general reaction conditions for the prenyl azides synthesis, compound **5** (34 mg; 0.23 mmol) was dissolved in anhydrous toluene (1 mL). Then, DPPA was slowly added (79 mg, 0.30 mmol) followed by the addition of DBU (46 mg; 0.30 mmol). After 8 h of continuous stirring at room temperature, the reaction was worked up and purified to afford 36 mg of colourless oil (isolated yield: 91%). ^{1}H NMR ($CDCl_3$): δ 7.42 ppm (m, 2H, *meta* aromatics, C3–H and C5–H); 7.32 (m, 3H, *ortho* and *para* aromatics, C2–H, C4–H and C6–H); 5.88 (dt, 1H, $^3J_{H8-H9} = 6.7$ Hz and $^4J_{H8-H10\ trans} = 1.3$ Hz, C8–H); 3.99 (d, 2H, $^3J_{H9-H8} = 6.7$ Hz, C9–H) and 2.12 (d, 3H, $^4J_{H10-H8} = 1.3$ Hz, C10–H). ^{13}C NMR ($CDCl_3$): δ 142.4 ppm (C1, *ipso* aromatic); 141.4 (C7, quaternary olefinic); 128.4 (C3 and C5, *meta* aromatics); 127.7 (C4, *para* aromatic); 125.9 (C2 and C6, *ortho* aromatics); 120.2 (C8, CH olefinic); 48.6 (C9, N–CH_2–) and 16.3 (C10, CH_3). IR (film): υ_{max} (cm^{-1}) 2976 (˙CH–), 2928 (–CH_2–), 2095 (–N3), 1623 (C=C).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors wish to express their gratitude to UNR (Universidad Nacional de Rosario), Fundación Josefina Prats, CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas, PIP 2009-11/0796 and PIP 2012-14/0448), Agencia Nacional de Promoción Científica y Tecnológica (PICT-2011-0589). MMV thanks UNNE, SECYT-UNNE (PI F005-2013), and ANPCyT (PICT-2015-2635). This investigation also received financial support (through GRL) from the UNICEF/UNDP/WORLD BANK/WHO Special Programme for Research and Training in Tropical Diseases (TDR). GRL, MMV and ABJB are members of the Research Career of CONICET. EOJP thanks CONICET for the award of a Fellowship.

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