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Synthesis of polymerizable vinyltriazoles: development of an optimized one-pot strategy starting from 4-bromobutyne†

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The development and implementation of a safe and scalable process for the preparation of isomeric vinyl-1,2,3-triazoles under mild conditions are described. Key aspects of the route reside in a one-pot click-elimination procedure in aqueous media leading to simple work-up and purification steps with increased overall yields.

4-Vinyl and 5-vinyl-(1*H*)-1,2,3-triazoles represent interesting classes of heterocyclic compounds and have received increasing attention in the field of polymer sciences, since it has been shown that 4-vinyl and 5-vinyl polymerizable monomers are valuable building blocks for the construction of well-defined macromolecules.[1–3] However, until recently, preparation of such monomers occurred only through multistep procedures, and the remaining challenge of this class of monomers resides in a simple and low-cost synthetic accessibility to large amounts with high degrees of functionalization. Three main multistep approaches using catalyzed azide–alkyne cycloadditions have been developed to date. The "Wittig approach" is based on a three-step procedure using propargyl alcohol as a starting material, which is converted to an aldehyde as a key intermediary for the Wittig step, allowing obtention of the vinyl derivatives in 60–75% yield.[4] The "vinylacetylene approach", in which the starting materials are trimethylsilylacetylene and vinyl bromide, is a two-step methodology where the crucial intermediary trimethylsilylvinylacetylene was obtained in 67% yield and the desired 4-vinyltriazole in the range of 44% from commercially available vinyl bromide. In addition, this methodology could not be applied to 5-vinyltriazoles.[3,5] In the "two steps click-elimination approach", the starting material is but-3-yn-1-ol, and the vinyl group is introduced by means of an elimination process from a mesylated intermediary leading to 4-vinyl and 5-vinyl derivatives.[6] However, when regarding the total yields from commercially available alkynes, yields remain poor, in particular for the 5-vinyl-(1*H*)-1,2,3-triazoles (Fig. 1).

As a part of our studies aimed at the elaboration of environmentally friendly antifouling coatings, here we are interested in the preparation of natural product-derived (1*H*)-1,2,3-triazoles possessing potent and non-toxic antibiofilm properties in view of the preparation of original polymers derived from these bioactive heterocycles.[7–9] For this purpose, low price, easily accessible large amounts of polymerizable bio-inspired triazole monomers are needed in a "green" approach in order to assess the most ecofriendly route to the final coatings.

Considering these elements, and in order to improve the preparation of such monomers, we report here an original synthesis of isomeric substituted 5-vinyl-(1*H*)-1,2,3-triazole and 4-vinyl-(1*H*)-1,2,3-triazole monomers that would be amenable to scale up, by means of a simple one-pot procedure from the commercially available 4-bromobutyne (Fig. 2).

In practice, we postulated that an elimination process from the intermediary bromo derivatives should be favored since the resulting vinyl compounds are conjugated with the triazolic ring. The first step of this work was to validate the concept of this one pot click-elimination process. For this purpose, compound **2** was prepared by reacting 4-bromobutyne and azide **1**[9] in EtOH/H_2O in the presence of $CuSO_4{\cdot}5H_2O$ as a catalyst. Without further addition of base (entry 1), **2** was isolated in 95% yield and characterized by ^{1}H-NMR, ^{13}C-NMR and mass spectra. For the elimination step, we postulated that the use of sodium hydroxide should permit the simplest work-up process through a simple extraction with ethyl acetate (Scheme 1).

Parameters of temperature, nature and concentration of sodium hydroxide were examined (Table 1) under different entries. The appropriate azide (0.4 mmol) was added to a solution of H_2O/EtOH (2 mL/2 mL) containing $CuSO_4$–$5H_2O$ (0.01 eq.), 4-bromobutyne (1.5 eq.) and sodium ascorbate (0.03 eq.). The resulting mixture was stirred for 12 hours at RT. The base (appropriate concentration, see entries 2–14) was added and the resulting mixture was stirred at the appropriate temperature for 8 hours. The resulting solution was extracted 3 times with ethylacetate. The organic layers were then dried

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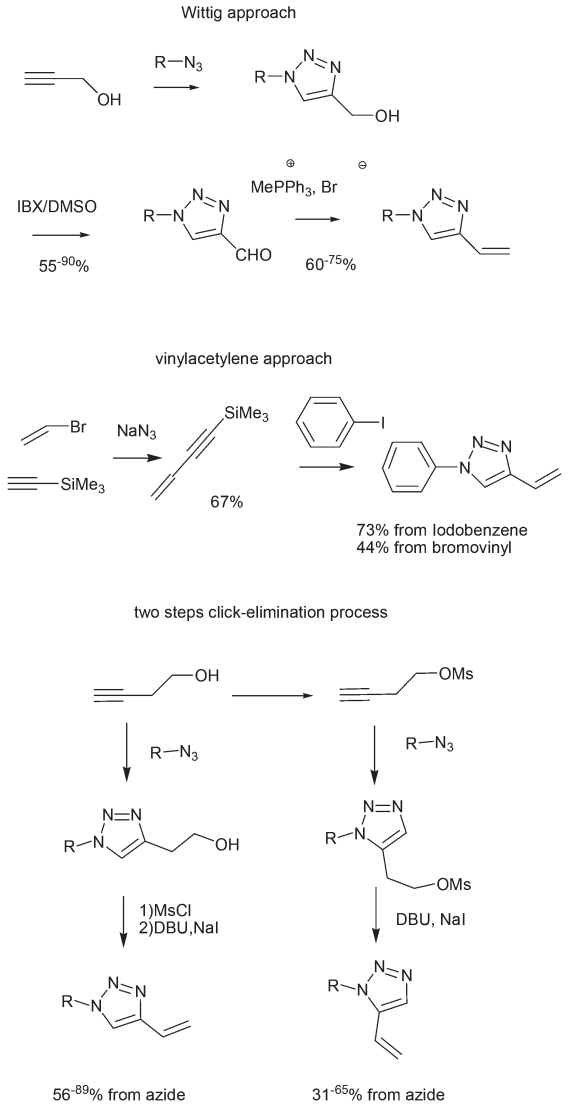


Fig. 1 Wittig, vinyl acetylene and two-steps click elimination processes.

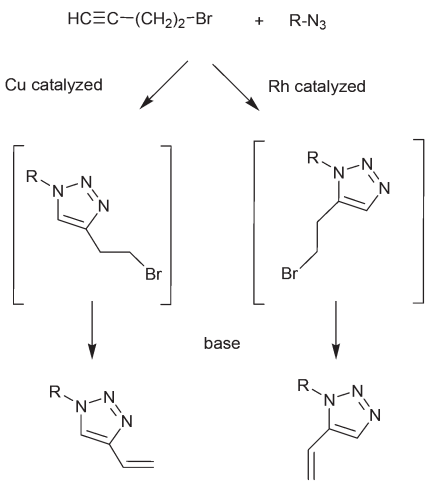
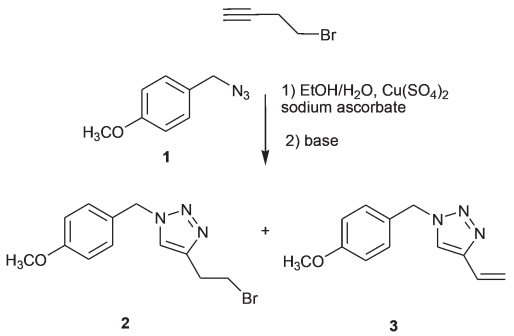


Fig. 2 Proposed one-pot two steps strategy for the preparation of 5-vinyl and 4-vinyl targeted triazoles.



Scheme 1 Preparation of **2** and/or **3** through the one-pot "click-elimination" process.

Table 1 Effect of reaction conditions on the preparation of **3** through the one-pot "click-elimination" process

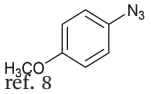
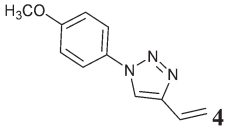
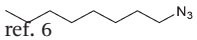
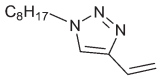
Entry[a]	Base		Temp.	Compound **3** yield (%)	Compound **2** yield (%)
1	—		25 °C	0	95
2	NaOH	5 eq.	25 °C	60	30
3			45 °C	82	Traces
4			60 °C	70	—
5			100 °C	75	—
6	NaOH	1 eq.		0	85
7		2.5 eq.		5	80
8		7 eq.	45 °C	92	—
9		10 eq.		99	—
10	DBU	2.0 eq.		53	25
11		5 eq.	45 °C	66	Traces
12		10 eq.		74	Traces
13	NEt_3	5 eq.	45 °C	11	67
14	LiOH	5 eq.	45 °C	84	—

[a] All reactions were conducted with 1.5 eq. of bromobutyne and yields were calculated from 1 eq. of azide.

over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel (Si60 15–40 μm), *n*-hexane/ethyl acetate (70/30)) gave the vinyl derivatives. In entries 2–5, the effect of temperature was first attempted using five equivalents of a base. At room temperature (25 °C), the conversion of compound **2** was incomplete and the desired vinyl derivative **3**[10] was obtained in 60% yield admixed with the bromo-derivative **2** (30% yield). At a temperature of 45 °C a good conversion of the intermediary brominated species to the vinyl derivative was observed (82% from azide). Augmentation to 60 °C and 100 °C led to lower yields (70 and 75% respectively), and no bromoderivative **3** was recovered, indicating a probable degradation of compounds at these high temperatures. Finally, the temperature of 45 °C was selected for the following experiments. In entries 6–9, we examined variations of the base concentration (1.0, 2.5, 7.0, and 10 equivalents of NaOH). The conversion rate was very low with 1 and 2.5 eq. and a conversion of 92% and 99% was observed with higher concentrations. From these experiments, the good compromise finally appeared to be a temperature of 45 °C, and the concentration of 5 equivalents of sodium hydroxide should be recommended to ensure mild conditions of the elimination

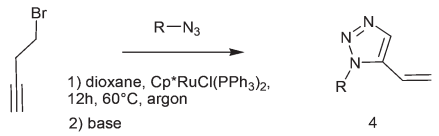
process. In entries 10–12, the nature of the base was investigated by using 2.0, 5.0, and 10 equivalents of 1,8-diazabicyclo-[5,4,0]undec-7-ene (DBU) which was the base used in the previously described two-step click-elimination approach.[6] No improvement of the elimination step was found. Finally, the use of triethylamine (entry 13) did not allow better yields (11% of conversion), while replacement of sodium hydroxide by lithium hydroxide (entry 14) led to a similar result (84%).

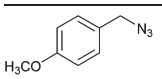
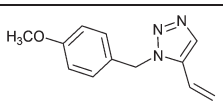
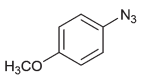
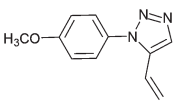
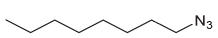
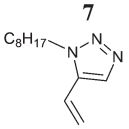
Table 2 Preparation of 4-vinyl-(1*H*)-1,2,3-triazoles

Azide	Triazole	Yield[a] (%)
 ref. 8	 **4**	88
 ref. 6	 **5**	86

[a] Conditions of entry 3 (5 eq. of NaOH), yield calculated from azide.

Table 3 Preparation of 5-vinyl-(1*H*)-1,2,3-triazoles



Azide	Triazole	Yield[a,b] (%)	
	 **6**	97[a]	56[b]
	 **7**	62[a]	NT[c]
	 **8**	59[a]	NT

[a] Conditions of entry 3 (5 eq. of NaOH), yield calculated from azide. [b] Conditions of entry 11 (5 eq. of DBU), yield calculated from azide. [c] NT: not tested.

The scope of the reaction was tested with two other azido compounds showing efficiency of the procedure with yields up to 85% for **4** and **5** (Table 2).

Then, we were curious to apply our methodology to the synthesis of the isomeric 5-vinyl-(1*H*)-1,2,3-triazoles. In this case too, treatment of bromobutyne in dioxane with the appropriate azide in the presence of catalytic amounts of $Cp^*RuCl(PPh_3)_2$ followed by basic treatment led to the formation of the desired 5-vinyl derivative **4**. Reactions were conducted at 45 °C using a concentration of 5 eq. of base. DBU and sodium hydroxide were tested (Table 3). A solution of appropriate azide (0.4 mmol, purity monitored by ^{1}H-NMR), alkyne (1 eq.) in dioxane (0.5 mL) was added under argon to 3.5 mL of dioxane containing a catalytic amount of $Cp^*RuCl(PPh_3)_2$ (0.02 eq.). The resulting mixture was stirred for 12 hours at 60 °C under argon atmosphere. After cooling, an appropriate base (NaOH, entry 3 or DBU, entry 11) was added and the resulting mixture was stirred at 45 °C for 8 hours. The resulting solution was extracted 3 times with ethylacetate. The organic layers were then dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel (Si60 15–40 μm), *n*-hexane/ethyl acetate (70/30)) gave the vinyl derivatives. Results were unambiguous: using NaOH, compound **6** was obtained in 97% yield, while the use of DBU led to compound **6** in only 56% yield. For the two other derivatives **7** and **8**, despite the fact that yields remain in the same scale as in the previously described method,[6] the main interest resides in the one-pot procedure which affords a simpler process.

All these results indicate that this new process affords a more sustainable synthetic route to 4-vinyltriazoles and 5-vinyltriazoles and should have a great interest for scale-up development in a "greener" concept. In this way, Table 4 summarizes the improvement of the preparation of such monomers in terms of pot, atom and step economy (PASE: a concept which combines as many transformations as possible into a single reaction vessel, without need for work-up and isolation of intermediate compounds).[11] Clearly, the three previously described methods implement organic solvents, additional carbon sources, catalysts, and finally organic bases to proceed with the elimination step. In the present methodology, the use of the combination H_2O–NaOH offers a pot economy

Table 4 Comparison of the different methods showing the green process of the present methodology

Starting material[a]	Solvents[b]	Reactants[b]	Pots[c]	Steps[c]	Applicability
Propargyl alcohol	DMSO, THF	$MeP^+(PPh_3)_2$, Br^-, IBX, NaH	3	3	4-Vinyl
Trimethylsilylacetylene	THF	TBAF, $PdCl_2(PPh)_3$, vinylbromide, NEt_3	2	2	4-Vinyl
But-3-yn-1-ol	DMF[d]	CH_3SO_2Cl, DBU, NaI	3	4	4 and 5-Vinyl
4-Bromobutyne	H_2O	NaOH[e]	1	2	4 and 5-Vinyl

[a] Carbon source of triazole ring. [b] The click step is not included since the reactants are the same for all methods. [c] Whole process including the click step. [d] Alternatively DME. [e] Alternatively DBU.

(reduction of solvents used in synthesis and work-up) and a step economy is realized (reduction of the amount of reagents by reducing the number of steps). The atom economy (FW product/FW of all reagents used) has been increased on average by 30% to 83% (31% to 83% when compared to the previously described two-steps click-elimination process and the present process; only NaOH is used without an additional source of carbon and/or other elements).

In conclusion, we have described a new process for easy preparation of 4-vinyl and 5-vinyltriazoles from 4-bromobutyne. Interest in the process focused on the one-pot "click-elimination" methodology. This procedure provides a new significant "greening" synthesis of vinyltriazoles with improvements in terms of yields, and operability when compared to previous methodologies. In particular, the use of a mineral base leads to an easier work-up process for further purifications and permits a facile scale-up of the methodology for a large diversity of azido compounds, while an organic base such as DBU remains usable, especially for substrates that are sensitive to hard mineral bases.

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