

High pressure assisted 1,3-dipolar cycloadditions: formation of 1,2,3-triazoles from aryl azides and (trimethylsilyl)acetylene



Valeria Melai,^a Aldo Brillante^{*a} and Paolo Zanirato^{*b}

^a *Dipartimento di Chimica Fisica e Inorganica and* ^b *Dipartimento di Chimica Organica 'A. Mangini', Università di Bologna, viale Risorgimento 4, I-40136 Bologna, Italy*

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The cycloaddition of aryl azides to the corresponding 1,2,3-triazoles has been studied by means of FTIR spectroscopy in a diamond anvil cell at pressures up to 1 GPa. The rate of reaction increases logarithmically with pressure and the yield is close to quantitative.

Introduction

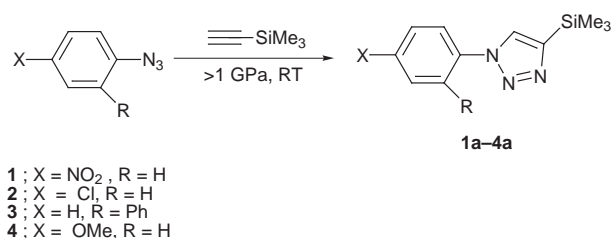
It is well established that in chemical transformations pressure will usually favor product formation whenever a higher density phase is established.¹ A large variety of examples can be found in the literature.² However steric effects are no less important and have been shown to be the driving factor in some interesting photophysical transformations.^{3,4} Among the whole body of organic syntheses, much attention has been devoted to cycloadditions, as typical cases of reactions with sizable negative activation volumes. The classical example is the Diels–Alder reaction, for which a quantitative treatment of the kinetic response to pressure is available.¹ Other cycloadditions, *i.e.* [2 + 2] and 1,3-dipolar, have also been shown to be significantly affected by pressure.⁵

Among the 1,3-dipolar cycloadditions, we have studied an interesting class of reactions starting from a series of aryl azides, whose reactions with neat (trimethylsilyl)acetylene lead to the formation of the corresponding triazoles in quantitative yields.⁶ The synthesis of 1,2,3-triazoles is important because of their extensive use in industry and agriculture.⁷ In the present study we show that under moderate external pressure (below 1 GPa) the product is formed in a few hours at room temperature, *i.e.* orders of magnitude faster than the corresponding transformations at ambient conditions. We have also quantitatively estimated the effect of pressure on the reaction rate for one specific reaction, finding a logarithmic dependence of the reaction rate with pressure. This result is a promising step toward a viable synthesis of those triazoles requiring thermally unstable reactant adducts such as, for instance, 2-azido-heteroaryls.⁸

Experimental

Reactions under pressure were carried out in a diamond anvil cell (DAC) using an excess of (trimethylsilyl)acetylene both as reactant and hydrostatic pressure medium. The advantage of using a DAC is that only a tiny quantity of material is required, typically a few hundreds of nanoliters. Pressures were measured with the ruby fluorescence method⁹ at the beginning of the reaction. During the course of the reaction the precipitation of the product leads to quasi- and eventually to non-hydrostatic conditions, preventing an accurate measurement of the external pressure. The transformation of aryl azides to 1,2,3-triazoles, widely illustrated in the literature,¹⁰ occurs according to Scheme 1.

Four different aryl azides (ArN₃) were tested in the above reaction, with Ar = *p*-nitrophenyl **1**, *p*-chlorophenyl **2**, biphenyl



Scheme 1

3, *p*-methoxyphenyl **4**, to give the corresponding 1,2,3-triazoles (**1a–4a**).

The reaction was followed by means of FTIR spectroscopy, recording the change of the spectrum of the reaction mixture at different values of time and pressure. By comparison with the IR spectra of the pure reactants, as well as those of the products, the course of the chemical transformation could be seen easily. Mass spectra were obtained, as needed, for further characterization of the products.

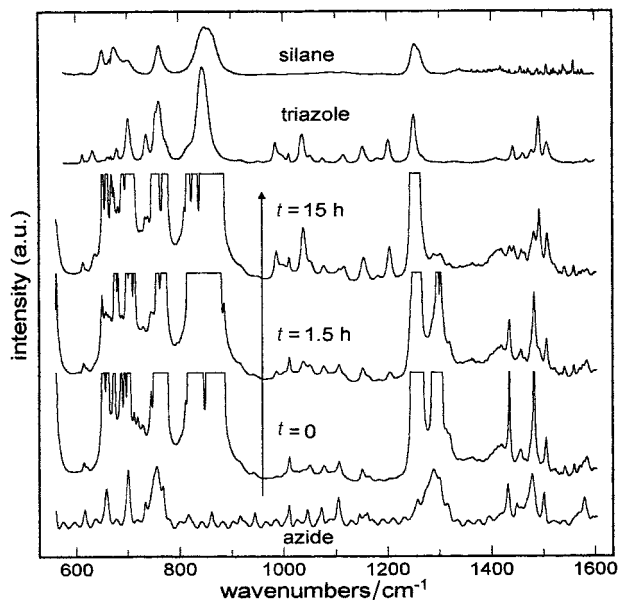
Results and discussion

The reaction mixture was monitored as a function of time at constant pressure by following the evolution of IR spectra. The reaction was considered complete when the spectral profiles showed no further change and were almost identical to the spectra of products taken separately on pure triazoles in KBr pellets. Since the diamond windows are not transparent to the most significant region of the N=N stretching, we examined the whole IR spectrum, with particular attention to those spectral regions transparent to the absorption bands of the excess silane. A typical example of how the reaction could be easily followed in this way is given in Fig. 1, for azide **3** at *P* = 0.2 GPa. In all cases the qualitative trend at high pressure showed a striking acceleration of the reaction rate, as compared to values found at 298 K and ambient pressure.⁶ A summary of the data is given in Table 1.

The data reported in the last column of the table are mostly qualitative and in no way imply that the reaction is complete, except that most features of the original bands of the azide have disappeared, at the sampled pressure, and new bands attributed to the triazole appear. It is clear that even moderate pressures, *i.e.* a few hundred MPa, speed up the chemical transformations by two orders of magnitude or more, and that the reaction yield is close to quantitative. For additional insight into the effect of pressure on the rate of reaction, the following approach was used.

Table 1 Room temperature times for aryl azides 1–4 at ambient pressure (P_0) and at selected pressure (P_i)

Compound no.	Aryl	Time/days (at P_0)	Pressure/GPa (at P_i)	Time/hours (at P_i)
1	<i>p</i> -Nitrophenyl	20	0.1	2
2	<i>p</i> -Chlorophenyl	25	<0.1	4
3	Biphenyl	35	0.2	<15
4	<i>p</i> -Methoxyphenyl	55	0.3	1.5

**Fig. 1** A typical example FTIR spectrum of the reaction mixture as compared to blanks of reactants and products. The reaction refers to azide 3 at 0.2 GPa.

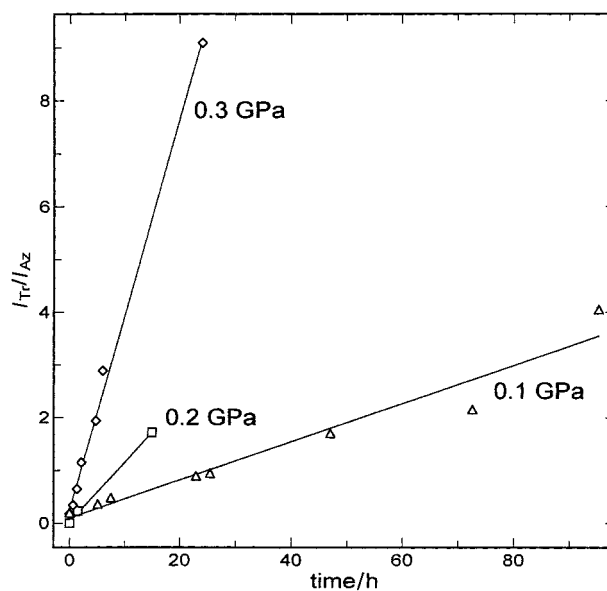
The pressure dependence of reaction rate

A quantitative determination of the rate of reactions of cycloadditions of azides to triazoles requires measuring the change of concentration of reactants and products as a function of time and pressure. For this study we had to use azide 3, since it is the only one yielding a triazole still liquid at room temperature, therefore retaining hydrostatic conditions in the DAC during the whole course of the reaction. For this azide we utilized four different pressures in the range 0–1 GPa, following for each of them the evolution of the FTIR spectrum of the reaction mixture with time and comparing them with the spectra of the pure reagents, azide (Az) and silane (Si), and the product, triazole (Tr), taken separately as blanks. We have sampled several spectral regions where bands of Az and Tr appear close to each other. From the deconvolution of the spectral profiles we derived the relative intensity ratio $I_{\text{Tr}}/I_{\text{Az}}$, a quantity useful to monitor the course of the reaction. In the case of azide 3 we chose bands in the range 1050–1150 cm^{-1} (see Fig. 1). Although we do not know the exact concentration of the individual species, the intensities (I_{Az} and I_{Tr}) of the IR bands, in selected spectral ranges, are approximately proportional to the concentrations of Az and Tr, [Az] and [Tr] respectively, with a being the proportionality constant. In an excess of silane, [Si] is constant, and reaction (1) becomes pseudo-first order.



It can be assumed that eqn. (2) applies to the reaction. In the

$$I_{\text{Tr}}/I_{\text{Az}} = a[\text{Tr}]/[\text{Az}] = a[A_0][1 - \exp(-kt)]/[A_0][\exp(-kt)] = a[\exp(kt) - 1] \quad (2)$$

**Fig. 2** The effect of pressure on reaction rate. Δ 0.1 GPa; \square 0.2 GPa; \diamond 0.3 GPa.

case of these cycloadditions, the rate constant k is very small (typically $\sim 10^{-7} \text{ l mol}^{-1} \text{ s}^{-1}$ at 25 $^{\circ}\text{C}$),^{10a,b} $\exp(kt) = (1.0 + kt)$ and $a[\exp(kt) - 1]$ therefore reduces to $\sim a[kt]$. The relative intensity of selected bands of Tr with respect to those of Az should yield linear relationships with a slope proportional to the rate constant. This is what is shown in Fig. 2, where linear plots are found for $P = 0.1, 0.2$ and 0.3 GPa. Values of the last experiment at 0.9 GPa are not plotted as at this pressure we observe an almost instantaneous transformation to the triazole. Fig. 2 clearly shows the striking effect of pressure on the reaction rate even in a moderate pressure regime as that within 1 GPa. The actual rate constant, k , can be derived by determining the value of a from calibration of IR spectra at ambient conditions of the two species. Fig. 2 also shows that 1 GPa represents a sort of threshold above which aryl azides immediately transform to the corresponding 1,2,3-triazoles.

In order to check whether a logarithmic relationship of the rate constants with pressure also holds for this class of reactions, we show in Fig. 3 a plot $\ln(ak)$, from the slope in Fig. 2, vs. pressure. The result confirms this expectation and compares well with the classical Diels–Alder results reported in ref. 1.

Conclusions

We have reported an example of organic reactions whose yield is strongly affected by pressure, up to the limit (~ 1 GPa) where the transformation is almost instantaneous and quantitative. This threshold pressure is surprisingly low with respect to available examples of cycloaddition under pressure.^{1,2} Interfacing the DAC with a FTIR is shown to be a very suitable technique for testing the evolution of reactions without the need of sizable quantities of reactants. Due to the low pressures involved, the use of larger vessels^{1,11} can lead to useful amounts of products for those organic syntheses otherwise inefficient at ambient

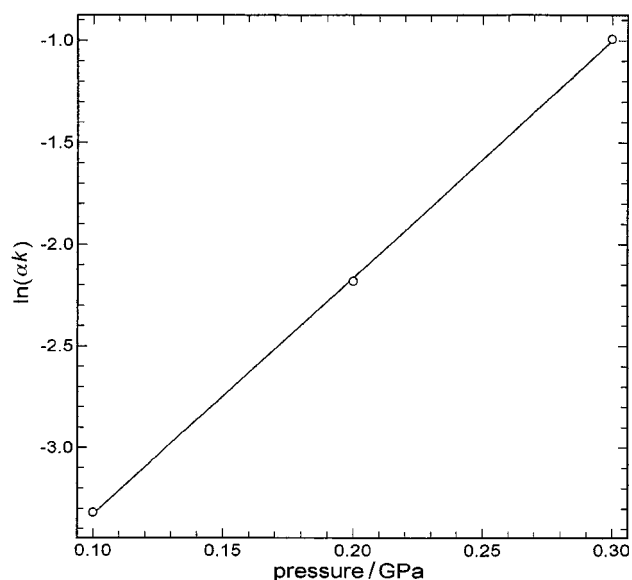


Fig. 3 Pressure dependence of reaction rate at room temperature. The response is logarithmic.

conditions. The thermally unstable 2-azidoheteroaryls for 1,3-dipolar additions to triazoles are an example.

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