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FULL PAPER

Monitoring of Reactions on Solid Phases *via* Raman Spectroscopy

Irina Protasova[a], Stefan Heißler[b], Nicole Jung[a,c]* and Stefan Bräse[a,c]*

Abstract: The benefits of Raman spectroscopy were shown for the on bead monitoring of diverse reactions. Raman spectroscopy was used for the development of new procedures on established linker systems, the real-time observation of several reactions on solid phases and the estimation of the reaction time for a new cleavage strategy. Selected conversions on solid phases like the on-bead conversion of functional groups and the attachment of novel building blocks were demonstrated. Raman spectra were gained after isolation and purification of the solid supports but they were also measured directly in the reaction vessels. Even the detection of Raman-active functionalities in swollen polymer resins and in reaction mixtures were proven, allowing the real-time observation of the progress of diverse reactions on solid supports.

Introduction

Solid phase organic synthesis (SPOS), playing an important role in combinatorial chemistry,[1-3] peptide synthesis[4-6] and drug discovery,[7-8] suffers from a lack of analytical methods for on-bead analysis of solid supported reactions. While the traditional use of solid phase chemistry deals with repetitive coupling reactions with amino acids, nucleotides or sugars to give peptides, nucleic acids or oligosaccharides respectively, modern applications of solid-supported reactions include the development of new methods for the syntheses of e.g. heterocycles[9-11] and natural products.[12-14] Especially for the latter purposes, the monitoring of the reaction and the identification of the target compounds on solid supports is of major importance. The traditionally used procedures for the identification of compounds like elemental analysis or cleavage cause drawbacks in solid phase chemistry due to the loss of material and are nowadays replaced or supplemented by new techniques for the on-bead analysis of reactions. The most important methods, offering several advantages as non-destructive analysis, have been introduced with the development of the gel-phase NMR-analysis,[15-16] the use of MAS-technology[17-18] or special applications as the ^{19}F NMR control of reactions *via* introduction of fluorine linkers.[19-20] Besides those opportunities *via* the use of (gel phase) NMR-techniques, IR and Raman measurements of which both offer the advantages of very fast measurements have been used for the control of reactions on polymeric material.[21-24] While the IR analysis has already found its way into the standard-procedures allowing the control of solid phase reactions[25-27] and for selected examples the monitoring of the reaction progress,[27-31] Raman (and SERS) technology has been, probably due to the low availability of Raman instruments, reported only in a few applications for the identification of small compounds on solid phases.[32] Amongst the latter experiments, almost all studies deal with investigations of material adsorbed on solid surfaces.[33-37] Other examples showing the utility of FT-Raman investigations are known for epoxy resins[38-39] and diverse other resins.[40-45] Selected examples showing the application of Raman techniques for peptide[46-48] and flow syntheses[49] or indicate the scope of the Raman technique especially due to the fast conduction of the experiments and the tolerance of water as solvent or impurity. During our studies on diverse reactions on solid supports where we faced the ongoing challenge to provide suitable tools for a fast analysis of the resulting immobilized compounds, we found Raman measurements to allow fast and reliable interpretation of the reactions. With a proper choice of functional groups and the implementation of a suitable model system, we were able to develop beneficial procedures for the on-bead analysis of solid supported reactions.

Results and Discussion

Proof of reaction concepts *via* Raman spectroscopy (Part 1)

Aiming for the development of a fast and reliable protocol for the interpretation of reactions on solid phases we explored techniques that allow either the direct visualization of the reaction on bead or the more general investigation of reactions *via* the use of a suitable model system. As the monitoring of unknown procedures on solid phases is of crucial interest at several stages of the synthesis from the attachment of the first building block to the cleavage of the target compound, our first investigations covered the observation of the immobilization of building blocks on commercial functionalized resins. Two of the most common polymeric starting materials namely sulfonyl chloride resin (**1**) and Merrifield resin (**2**) were used to show that Raman technology offers on the one hand the opportunity to determine the necessary requirements for new synthetic techniques (e.g. the immobilization of ketoximes to a sulfonyl chloride resin)[50] and that Raman spectroscopy allows on the other hand to reconsider the reaction parameters of well-known reactions as the triazene linker formation. Therefore, Raman spectroscopy was used to establish the attachment

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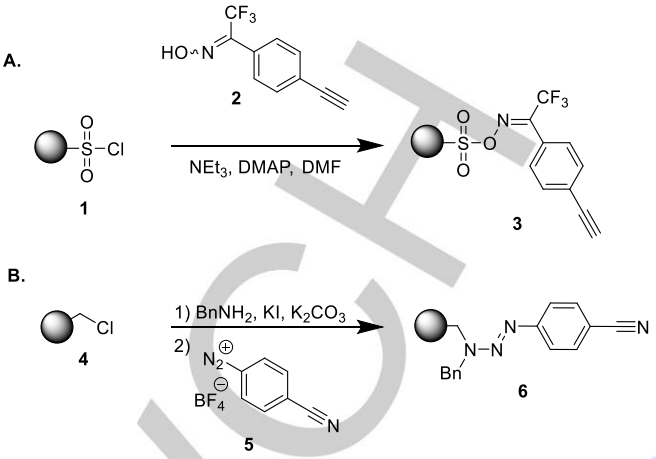
of ketoxime building blocks onto a commercially available resin *via* alteration of the reaction conditions. The application of an alkyne bearing ketoxime has been shown to be beneficial since alkynes can be identified easily due to their distinct and strong peak at an isolated position in the Raman spectrum (1800–2800 cm^{-1}). The monitoring of the reaction with different additives, solvents and under various temperatures has been performed *via* isolation and measurement of a small sample of the dried resin. After normalisation of the resulting spectra using an aromatic C-H vibrational band arising from the solid support that was used as internal standard (3061 cm^{-1}, see also Table 1, A), we were able to compare the obtained results. The most suitable procedure for the formation of **3** according to the obtained Raman spectra was a conversion of the starting material **1** with ketoxime **2** with a combination of Et_3N and DMAP as base in DMF as solvent (Scheme 1 and Figure 1, example A). The intensity of the normalized alkyne band (2112 cm^{-1}) was shown to stack at its maximum value after a reaction time of 5 h. A similar procedure was used for the determination of the reaction time for the attachment of diazonium salts to immobilized amines to give triazene linkers.[51-53] The latter reaction is well-known as a prominent procedure for the synthesis of diverse heterocycles[54-56] or the introduction of valuable functionalities to an aromatic building block.[57-60] We adapted the above described method using alkynes to a very similar approach using nitriles, which are more suitable building blocks for the reactions as they are non-expensive, commercially available reagents. It was demonstrated that the formation of the nitrile-bearing triazene **6** *via* coupling of 4-cyanobenzenediazonium tetrafluoroborate (**5**) with benzylamine resin (gained from Merrifield resin **4** in one step) can be used as model system to analyse the progress of the triazene forming reaction. The increase of the C≡N vibrational band at 2224 cm^{-1} was used to monitor the progress of the reaction and to determine the time that was necessary to achieve full conversion of the resin. Raman spectra of the reaction to nitrile **6** have been taken after reaction on solid supports for 30 min, 60 min, 120 min and 12 h at room temperature. To achieve contamination free spectra, the resins were washed thoroughly and were dried *in vacuo*. It was shown that a typical triazene-formation on solid supports (in 500 mg scale and with vigorous shaking) needs a reaction time of 30 min to be completed (Scheme 1 and Figure 1, example B).



Scheme 1. Alkyne and nitrile bearing resins for monitoring of building block attachment on solid phases.

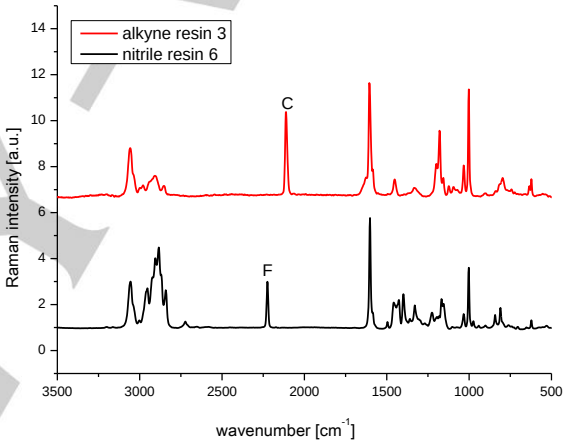


Figure 1. Monitoring of the successful immobilization of functionalized building blocks (see Table 1 for the assignment of bands C and F).

Real-time monitoring of transformations on bead using the reaction mixture (Part 2). Inspired by the very good results for the monitoring of the immobilization of building blocks on solid phases that offer important tools to prove the success of a reaction, we investigated the potential of Raman spectroscopy to enable real-time reaction monitoring. Due to the unique advantages of Raman spectroscopy, namely fast measurements in common reaction vessels and solvents with tolerance of water without the need for purification of the solid supported material, this often underestimated method reveals beneficial opportunities for the control of reaction. While the proof of concept-method with purified resins (Part 1) tolerates even reactants or solvents bearing alkyne or nitrile functionalities, real time monitoring of the reaction mixture (Part 2) works only if no other reagent interferes with the signals of the functionality to be investigated. Suitable systems that allow a real time monitoring on solid phases are therefore for example transformations that are used to generate or modify triple bonds.

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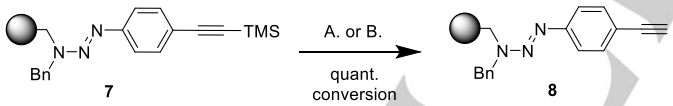
Monitoring of deprotection strategies for TMS-modified alkynes (Part 2.1).

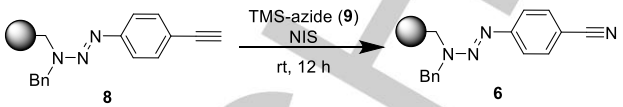
During our work with alkyne bearing solid supports we were often facing the need for the introduction and removal of a protecting group as trimethylsilyl (TMS). Literature known procedures, especially for similar approaches to remove the TMS group in solution, are available but information on a comparison of the different methods and their results on solid phases are lacking up to now. This is of particular interest for solid phase chemistry as the success of all transformations depends strongly on the nature of the linker unit which has to be proven to be stable during the reaction. Aiming for a comparative investigation of different TMS-deprotection strategies, resin **7** has been reacted using K_2CO_3 and TBAF as an alternative in parallel according to well-known standard reactions in solution (Scheme 2).[61,62] The transformation of an internal to a terminal alkyne allows the monitoring of the reaction *via* observation of a decreasing signal of the immobilized starting material (C≡C of TMS-alkyne: 2154 cm^{-1}, see Table 1) and an increasing signal of the nascent product signal (C≡C of alkyne: 2107 cm^{1}, see Table 1). The measurements were done directly in the reaction vessel where the solid supported material was furnished in a mixture of solvent and deprotection reagent. We were able to show that both, K_2CO_3 and TBAF, are suitable reagents for the cleavage of a TMS protective group on solid supports while keeping the triazene linker unit unchanged. The direct comparison reveals that the cleavage of TMS with TBAF on the solid support is superior to the use of K_2CO_3 under the chosen reaction conditions, as the TBAF-conversion is quantitative after 1 minute whereas the same result is obtained with K_2CO_3 only after 4 h.



Scheme 2. Deprotection of TMS-modified alkyne **7** on a triazene linker. Conditions: A. K_2CO_3, DMF, 4 h, rt; B. TBAF, THF, 1 min, rt.

Transformation of solid supported alkynes into nitriles (Part 2.2).

As investigations towards the differentiation of internal and terminal alkynes on solid supports were successful, we installed a linker unit to prove that a detection of an alkyne in the presence of a nitrile functionality is possible (Scheme 3). Such an analytical tool is suitable for the monitoring of the progress of nitrile to amine transformations or vice versa for the investigation of e.g. alkyne to nitrile conversion on solid phases.[56,63] To prove the benefit of real time Raman measurements for the control of the latter reaction, resin **8** was treated with TMS-azide (**9**) in the presence of *N*-iodosuccinimide (NIS). To the best of our knowledge, this reaction is herein shown for the first time on solid supports. It has been demonstrated that the reaction which was followed by the decrease of the alkyne vibrational band (2107 cm^{-1}, see Table 1) and the simultaneous increase of the nitrile vibrational band (2224 cm^{-1}, see Table 1) was completed after 12 h (Scheme 3, Figure 2).[60]



Scheme 3. Transformation of the alkyne **8** to the nitrile **6** on solid supports.

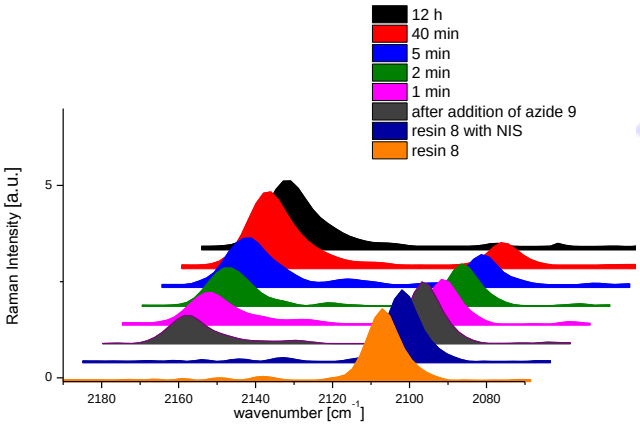


Figure 2. Real time monitoring of the on-bead transformation of alkyne **8** to nitrile **6** via Raman spectroscopy of the reaction mixture.

Diazonium chemistry on solid supports: Monitoring of diazonization reactions, stabilization of diazonium ions and their reactions on solid supports (Part 2.3).

Diazonium-salts are very prominent functionalities that offer unique transformations in organic chemistry such as the Balz-Schiemann reaction, Sandmeyer reaction or the formation of triazenes. The latter ones have been used extensively for the introduction of functional groups or heterocycle synthesis on solid supports.[51-60,65] To the best of our knowledge, the *in situ* nascence of the diazonium species has not been reported before *via* Raman or IR-spectroscopy although it is expected to be a suitable model system for real time measurements *via* vibrational spectroscopy due to its Raman-active N≡N triple bond. In order to monitor of the diazonization reaction and the stabilization of the resulting diazonium ions including their reactions on solid supports, we used the triazene T2 linker to demonstrate the scope of the herein described procedure. After the attachment of an aniline-based linker unit (**10**), the diazonium salt has been formed according to a standard procedure with $BF_3{\cdot}OEt_2$ and isoamyl nitrite in THF as a solvent (Scheme 4). By observation of the arising N≡N band (~2265 cm-1, see Table 1) we could show that the diazotization on solid phases was finished in less than one minute. The obtained immobilized diazonium tetrafluoroborates were further used to prove their ability to

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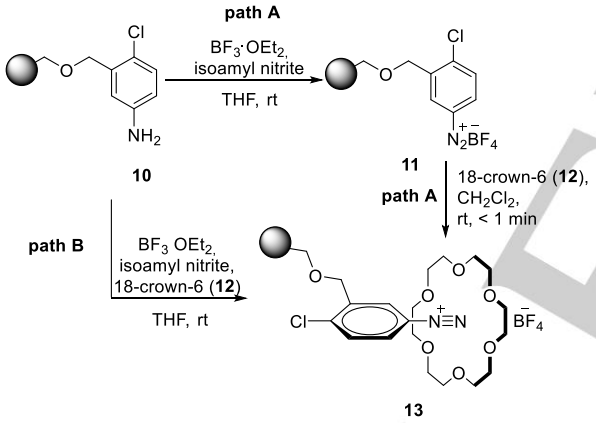
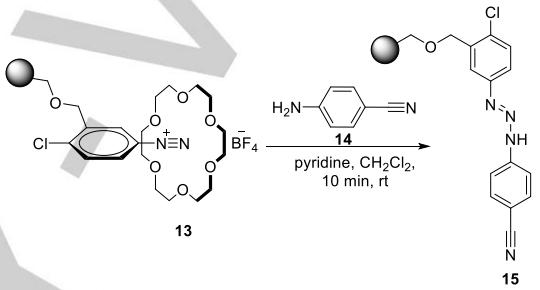
form stable complexes with crown ethers, which is a known procedure to overcome problems that origin in the instability of some diazonium salts.[66] While the stabilization of diazonium salts with 21-crown-7 ether is literature-known, we used the commercially available 18-crown-6 (**12**) for complexation experiments. Due to a slight shift of the crown-ether masked diazonium species **13** in comparison to the unmodified immobilized tetrafluoroborate **11**, we were able to visualize the formation of a resin bound complex of a diazonium salt with 18-crown-6 (path A, Scheme 4). The resulting complex **13** was formed in less than one minute (shift of the diazonium band from 2265 cm^{-1} to 2313 cm^{-1}) and was stable upon washing of the resin with toluene. The control *via* Raman spectroscopy revealed that purification of the resin with standard protocols for washing procedures of resins is not recommended as unmasking to the diazonium salt takes place during the treatment with alcoholic solvents. The synthesis of crown ether masked diazonium salts was shown additionally in an one pot procedure. The direct conversion of immobilized amines under diazotization conditions in the presence of 18-crown-6 resulted again in the formation of the masked diazonium salt **13** (path B, Scheme 4).



Scheme 4: Exemplarily chosen diazotization-masking protocol; path A: reaction of aniline **10** to the corresponding diazonium tetrafluoroborate **11** and subsequent masking with 18-crown-6 (**12**); path B: one-pot procedure to the target resin **13**.

In situ monitoring of azo coupling reaction of diazonium salts in case of T1 and T2 linkers (Part 2.4).

While the examples in Scheme 1 to Scheme 4 prove the immobilization of a linker to a solid support or the on-bead conversion of one functionality into another, the monitoring of the attachment of additional building blocks on the solid phases is possible as well. The only requirement for an *in situ* monitoring of the reaction is the presence of a Raman-active functionality on the novel building block. If the desired building block doesn't bear such a functionality, it is still possible to establish a standard model system to prove the general concept of the reaction with an e.g. alkyne or nitrile containing building block. The immobilized masked diazonium salt **13** that was presented in Scheme 4 has been chosen to demonstrate such a procedure. For this purpose, the resin **13** was used for the formation of triazenes on bead, a well-known reaction for e.g. non-complexed immobilized diazonium tetrafluoroborates. We could show that the triazene formation can be conducted also with complexed resins **13** using immobilized 4-aminobenzonitrile **10** as an aniline derivate and CH_2Cl_2 as solvent in the presence of pyridine (Scheme 5). The choice of an aniline bearing a Raman-active functionality allowed the monitoring of two indicators for a successful transformation on solid supports: the disappearance of the diazonium salt band on the one hand and the appearance of the nitrile band (2224 cm^{-1}, see Table 1) on the other hand. The reaction was shown to be finished within 10 min (Scheme 5).



Scheme 5. Reaction of the masked diazonium salt **13** to triazene **15**.

The example in Scheme 5 is used to demonstrate that the disappearance of signals of Raman-active compounds can be taken as an indication for the success of reactions as well. In those cases where no other characteristic signals arise during the derivation on bead, the result has to be controlled *via* additional analytical methods like a test cleavage. Such an example was proven *via* the addition of Grignard reagents or activated arenes to immobilized arene diazonium salts (Scheme 6) to form resin-bound azo derivatives. In a preliminary step, the conversion of an amine functionality into a diazonium tetrafluoroborate **17** was performed successfully on solid phases using aniline **16** which was attached to a T1 linker. The reaction was finished after 10 min which was assumed due to a stagnating increase of the nascent diazonium signal at 2247 cm^{-1}. As far as we know, this is the first example for the generation of a diazonium salt on the acid-labile triazene linker unit. The success of the reaction can be explained by the conditions of the reaction that allow a fast conversion of the starting material *via* diazotization while they do not induce a fast cleavage of the triazene bond. In a following step, the obtained diazonium salt was converted into different azo containing compounds **20a-c**. According to literature known protocols, methods including the use of arene Grignard compounds[67,68] (A, Scheme 6) or activated arenes[69] (classical Azo-coupling, B, Scheme 6) were used for the coupling reaction on bead in the past. The endpoint of the reaction was determined by the

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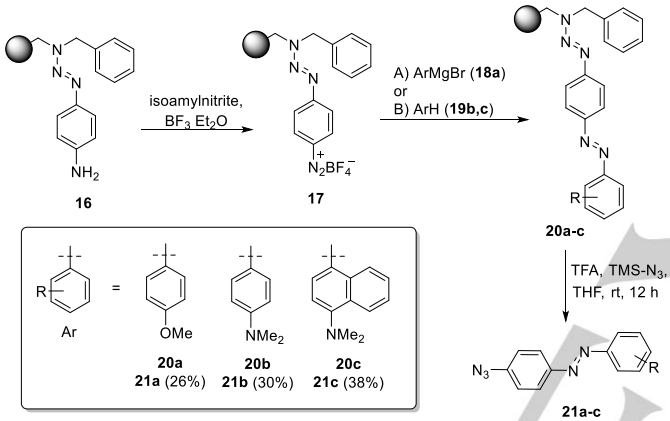
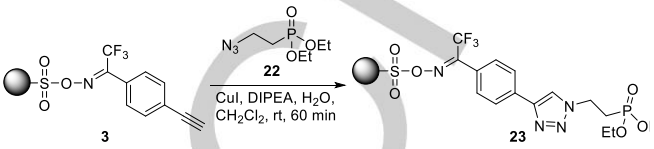
disappearance of the characteristic diazonium signal at 2247 cm^{-1}. The disappearance of the signal indicated the success of the conversion after 5 minutes. The azo coupling was also performed *via* addition of *N*,*N*-dimethylaniline (**19b**) and *N*,*N*-dimethylnaphthalen-1-amine (**19c**), to the immobilized diazonium salt **17.** The control of the reaction *via* Raman spectroscopy hypothesizes the end of the reaction after 30 min (for resin **20b**) and after 3.5 h (for resin **20c**) respectively, indicated by the absence of the initial signals at 2247 cm^{-1} and 1579 cm^{-1}. For all three resins (**20a-c**) the results of the on bead reaction monitoring were additionally proven qualitatively *via* cleavage and isolation of the resulting azo-containing compounds. Treatment of the resins with TFA in THF and addition of TMS-azide at room temperature provided the products **21a-c** in good to moderate yields calculated over 5 steps.



Scheme 6. Synthesis of azo-containing compounds **21a-c** on a triazene-linker.

Monitoring of Click reactions on solid supports (Part 2.5)

Another example for the monitoring of reactions through the disappearance of Raman signals on solid phases is the Click reaction of immobilized alkynes with azides, called CuAAC (copper(I)-catalyzed alkyne-azide cycloaddition). In a recent communication,[45] we introduced the solid phase mediated synthesis of diazirines, an important heterocyclic compound class in organic and bioorganic chemistry. The synthesis of a library of diazirine precursors has been gained *via* attachment of different building blocks on immobilized sulfonyloximes *via* CuAAC reaction (Scheme 7). The starting material **3** bearing an alkyne functionality was converted with different azides in the presence of CuI and DIPEA in a mixture of DMF/water. For exemplarily chosen examples, of which the reaction with diethyl (2-azidoethyl)phosphonate **22** is presented here, the progress of the reaction was shown *via* real-time Raman measurements of the reaction mixture. The benefits of the chosen analytical procedure are the visualization of the progress of the reaction directly in the reaction vessel in the presence of all reagents and solvents including water. Each of the Raman spectra has been gained *via* short interruption of the shaking process and measurement in distinct intervals up to a reaction time of 60 min (Scheme 7). The immobilized target resin **23** was gained after a reaction time of 60 min which was qualitatively proven by its cleavage with ammonia and the isolation of the resulting diaziridine (isolated yield of 50% over two steps[45]).



Scheme 7. CuAAC reaction with diethyl (2-azidoethyl) phosphonate **22** to resin **23**.

Real-time monitoring of transformations on bead in the presence of interfering reagents: monitoring of Sonogashira reactions (Part 3).

While conversions with Raman-active reagents in the reaction mixture can be monitored on solid supports easily *via* isolation of the solid supported material and measurement of the obtained intermediate (see e.g. Scheme 1 and Figure 1), the determination of the progress of a reaction in the presence of an excess of Raman-active reagents is more challenging. We chose one of the most important cross coupling reactions, the Sonogashira reaction, to prove the utility of on-bead Raman-spectroscopy for the monitoring of the progress of an alkyne-forming reaction on solid supports. Due to a lack of real-time monitoring procedures for the Sonogashira reaction on bead, former protocols have been published which use rather harsh reaction conditions (heating, reaction overnight) to be sure to gain quantitative conversion of the immobilized starting material.[55] Since the use of an excess of alkyne reagent in the reaction mixture is recommendable but hampers the signal detection, we examined the reaction in IRORI kans that allow the isolation of the solid supported material from the reaction mixture *via* simple removal of the kan. The Raman measurement was then conducted without further treatment in the IRORI kan including the swollen resin and residues of the reaction mixture. After the acquisition process, the IRORI kan was given into the reaction vessel for the continuing of the conversion. We could show that the conversion of an immobilized aryl iodide **24** (on a triazene linker) with ethynylbenzene (**25a**) or ethynyltrimethylsilane (**25b**) in the presence of CuI, $Pd(PPh_3)_2Cl_2$ and Et_3N in DMF was successful within 60 min at room temperature (Scheme 8, Figure 3). The observation of the progress of the reaction was possible due to an increasing signal at 2215 cm^{-1} corresponding to the formation of an internal alkyne, that wasn't affected by the intensive signal of the remaining terminal alkyne signals of the starting materials **25a** (2105 cm^{-1}) and **25b** (2213 cm^{-1}). Additional experiments on

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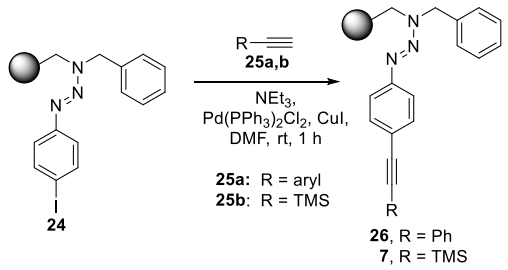
a similar linker system with an immobilized aryl bromide have been used for the determination of reaction conditions on solid phases with other aryl halides. In accordance with the literature, the latter reactions proved the need for higher temperatures in combination with a prolonged reaction time (80 °C, 24 h) for a complete conversion of the solid supported material.



Scheme 8. Sonogashira reaction of solid supported aryl iodide **24** with ethynylbenzene (**25a**) and ethynyltrimethylsilane (**25b**).

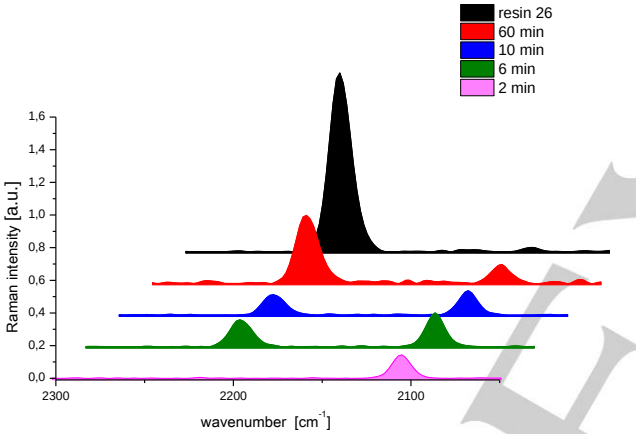
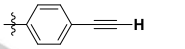
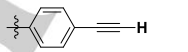
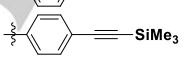
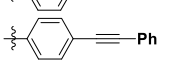
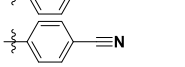
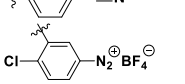
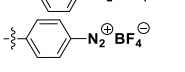
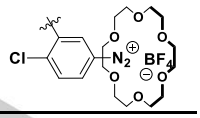


Figure 3. Real-time reaction monitoring of the Sonogashira reaction of solid-supported aryl iodide with ethynylbenzene (**25a**) to **26**.

Table 1. Summary of characteristic signals for selected solid supported functional groups.

Label[a]	No	Band [cm^{-1}]	Intensity* and assignment	Fragment
A	polymer	3061	- Ar. CH	internal standard polymer backbone
B	**3**	2112	vs C≡C	
C	**8**	2107	vs C≡C	
D	**7**	2154	vs C≡C	
E	**26**	2215	vs C≡C	
F	**6**, **15**	2224	s C≡N	
G	**11**	~2265	w - N≡N$^+$	
H	**17**	2247	w - N≡N$^+$	
I	**13**	2313	w - N≡N$^+$	

[a] * Intensity of the observed signal in comparison to the given standard (polymer, A), vs = very strong, s = strong, w = weak.[71]

Monitoring of cleavage reactions (Part 4)

While Raman experiments offer diverse benefits for the monitoring of on-bead conversions, Raman spectroscopy can also be used as a fast and sensitive method for the detection of the endpoint of a cleavage reaction under certain conditions. Whereas several alternative procedures suffer either from prolonged acquisition times (^{13}C-Gel NMR), low sensitivity (TLC control) or a lack of information (all methods that analyse the cleaved solution but do not analyse the remaining resin), Raman spectroscopy allows an estimation of the expected reaction time and the detection of residual amounts of immobilized material on the solid support. For a precise determination of the success of a cleavage reaction, the isolation and purification of the resin after distinct intervals is necessary, but very good evaluations can be obtained even without the isolation of the resin during the cleavage step. Following the IRORI kan method that has been described for the monitoring of the Sonogashira reactions in Scheme 8, we were able to identify the endpoint of a cleavage reaction from solid supports *via* short-term removal of the reaction vessel from the cleavage mixture and the measurement of the resin in the IRORI kan. The dilution of the cleaved product and its distribution within the crude cleavage mixture allows a good determination of the residual compound on solid phases even though the resin was not purified prior to the measurement. The procedure has been shown exemplarily using the immobilized alkyne **26** and its reaction with TFA in THF (Scheme 9). First experiments have been conducted at room temperature, showing that even after 3 h the intensity of the C≡C vibrational signal at 2215 cm^{-1} hasn't changed, revealing the inefficiency of the protocol at room temperature.[64,70] The cleavage was then repeated at 80 °C and Raman spectra were recorded after 1 min, 60 min and 3 h. It has been shown that after 3 h, only a very small signal of the alkyne functionality was retained. The latter signal vanished after single washing step of the treated resin confirming the assumption that it has to be assigned to the remainder of cleaved product in the supernatant solvent inside the IRORI kan.

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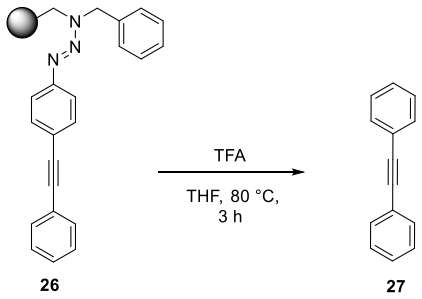
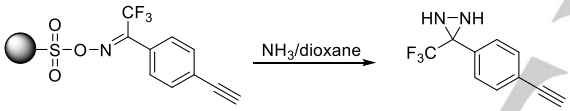


26 27

Scheme 9. Cleavage of arenes **27** from a triazene resin **26a** using TFA.

Other cleavage reactions and conditions have been reinvestigated by the use of Raman spectroscopy as a valuable tool for the optimization of reaction conditions. Especially reactions for which no other protocols are available on solid phases have been subjected to a Raman measurement since common protocols in solution are not transferable to the solid phases without adaptions. One of these reactions is the cleavage of the sulfonyloxime linker **3** with ammonia in dioxane. Here again, the change of the C≡C vibration band of the alkyne group has been observed for the detection of the end of the reaction using the non-purified swollen resin in a glass vial. For the latter conversion, the recorded spectra indicate the complete cleavage yielding the compound **24** after 12 h (Scheme 10).



3 24

Scheme 10. Cleavage of the sulfonyloxime linker **3** giving the target compound **24.**

Conclusions

Raman spectroscopy, offering several advantages for the analysis of resin bound compounds as fast acquisition time, tolerance of water and the measurement in diverse media, is still a rather unusual method for the monitoring of reactions on solid phases. We were able to show that the measurement of Raman spectra can be used for the development of procedures for novel linker systems and that it can be used for the monitoring of reactions on solid phases like the conversion of functional groups or the attachment of novel building blocks. Additionally, we could present two examples where Raman measurements allow the estimation of the reaction time during a cleavage of the target compounds from the solid supports. It has been shown that, depending on the requirements of the starting material and the reagents in solution, the acquisition of Raman spectra on solid supports is quite flexible: Raman spectra have been gained after isolation and purification of the solid supports but they have also been measured in reaction vessels like glass ware or IRORI kans respectively. Even the detection of Raman-active functionalities in swollen resins and in complete reaction mixtures was proven allowing the real-time observation of the progress of diverse reactions on solid supports. Since the utility of Raman spectroscopy relies on the presence of Raman active functionalities that are easy to identify even in mixtures with highly functionalized molecules, the use of the Raman technology has to be figured out in advance. Functionalities including a carbon-carbon or a carbon-nitrogen triple bond offer outstanding properties for their spectroscopic observation and are therefore highlighted in the present work but other functionalities might be useful targets for their visualization *via* Raman techniques as well. The herein described procedures show the use of Raman measurements for diverse applications on solid supports illustrating the potential to gain new insights into solid supported reactions. Using the herein described reactions and the concepts including Raman-active functionalities, solid phase chemists will be able to develop powerful model systems for the monitoring of their reactions on bead. Future applications of the herein described methods could be the on bead investigation of reactions in a combinatorial manner using the high throughput modules of modern Raman spectrometers in a 96 well format.

Experimental Section

Methods for the syntheses of triazenes, sulfonyl oximes and ether linkers on solid supports have been described earlier[50],[59],[65] and are given in detail for the selected examples in the Supporting Information. The general procedures and the single procedures, the description of the washing procedures for the isolation of solid supported material and Figures monitoring all conversions described in the Schemes are also given in the SI.

The control of the reactions *via* Raman spectroscopy was done according to four different procedures A-D.

Method A (measurements of neat material): After the end of the reaction the resin was washed by the general washing procedure and dried *in vacuo*. The measurement was carried out in an aluminum powder sample holder (Bruker Optics).

Method B (*in situ* measurements): The Raman spectra were taken directly from the reaction mixture without isolation of the resin und without any washing steps. Therefore the shaking of the reaction was interrupted and the vessel (glass vials were used) was placed into the sample compartment of the Raman spectrometer. Depending on the quantity of the available material, the reaction was carried out in a glass vial of 1.5 mL or 10 mL.

Method C (measurement in an IRORI kan): The reaction was carried out in an IRORI kan. Prior to the measurement, the shaking of the reaction was interrupted; the kan was removed from the reaction mixture and was washed once with the solvent

of the reaction. After the measurement the kan was returned to the remaining reaction mixture. The process was repeated until the complete conversion of the starting material has been monitored.

Method D (Measurement in a pretreated IRORI kan): The IRORI kan was isolated from the reaction mixture. The kan was placed on a sheet of paper to absorb the supernatant solvent.

1-(4-Ethynylphenyl)-2,2,2-trifluoroethanone oxime (**3**). Raman measurements were carried out according to methods A and C. Raman spectrum of the isolated target resin **3** (500 mW, 1064 nm), ṽ = 3058, 2908, **2112**, 1605, 1452, 1179, 1002 cm^{-1}.

4-(3-Benzyl-3-polystyrylmethyltriaz-1-en-1-yl)benzonitrile (**6**). The Raman measurement was carried out according to method A. Raman spectrum of the isolated target resin **6** (900 mW, 1064 nm), ṽ = 3056, 2953, 2905, 2884, 2723, **2224**, 1602, 1496, 1457, 1427, 1399, 1360, 13330, 1225, 1167, 1155, 1033, 1003, 974, 901, 842, 810, 622 cm^{-1}.

3-Benzyl-3-polystyrylmethyl-1-(4-((trimethylsilyl)ethynyl) phenyl) triaz-1-ene (**7**). The Raman measurement was carried out according the method A and B. Raman spectrum of the isolated target resin **7** (900 mW, 1064 nm), ṽ = 3054, 3002, 2901, 2852, **2154**, 1600, 1494, 1446, 1427, 1400, 1321, 1226, 1183, 1161, 1032, 1003, 801, 706, 622, 472, 412 cm^{-1}.

3-Benzyl-3-polystyrylmethyl-1-(4-ethynylphenyl) triaz-1-ene (**8**). Raman measurements were carried out according to methods A and D. Raman spectrum of the isolated target resin **8** (900 mW, 1064 nm), ṽ = 3055, 2988, 2944, 2836, **2107**, 1601, 1426, 1400, 1222, 1163, 1032, 1002, 740, 705 cm^{-1}.

4-Chloro-3-(polystyrylmethyl)diazonium tetrafluoroborate (**11**). Raman measurements were carried out according to methods A and D. Raman spectrum of the isolated target resin **11** (60 mW, 1064 nm), ṽ = 3054, 3002, 2979, 2900, 2851, **2265**, 1603, 1583, 1557, 1451, 1330, 1200, 1182, 1156, 1088, 1032, 1002, 913, 795, 704, 621, 286, 224 cm^{-1}.

4-Chloro-3-(polystyrylmethyl)diazonium tetrafluoroborate-18-crown-6-complex (**13**). Raman measurement was carried out according the method A. Raman spectrum of the isolated target resin **13** (60 mW, 1064 nm), ṽ = 3054, 3002, 2979, 2900, 2851, **2313**, 2287, 1603, 1583, 1557, 1451, 1330, 1200, 1182, 1156, 1088, 1032, 1002, 913, 795, 704, 621, 286, 224 cm^{-1}

4-(3-(4-Chloro-3-((polystyrylmethyl)methyl)phenyl) triaz-2-en-1-yl)benzonitrile (**15**). Raman measurement was carried out according the method A and B. Raman spectrum of the isolated target resin **15** (60 mW, 1064 nm), ṽ = 3064, 2964, 2952, 2927, 2906, 2884, 2867, 2838, 2723, **2224**, 1603, 1584, 1459, 1360, 1330, 1220, 1183, 1154, 1126, 1104, 1035, 1002, 974, 941, 901, 841, 810, 767, 639, 622, 527, 456, 456, 399, 321, 294, 226, 176, 106 cm^{-1}.

3-Benzyl-3-polystyrylmethyldiazonium tetrafluoroborate (**17**). Raman measurements were carried out according the methods A and B. Raman spectrum of the isolated target resin **17** (60 mW, 1064 nm), ṽ = 3055, 2984, 2965, 2952, 2926, 2905, 2884, 2867, 2841, 2718, 2651, 2279, **2247**, 1604, 1579, 1460, 1377, 1332, 1296, 1251,1221, 1170,1154, 1088, 1033, 1002, 974, 941, 900, 842, 810, 741, 705, 648, 622, 530, 492, 459, 400, 321, 287, 177, 107 cm^{-1}.

3-Benzyl-3-polystyrylmethyl-1-(4-((E)-(4-methoxyphenyl) diazenyl)phenyl) triaz-1-ene (**20a**). Raman measurements were carried out according to method A and B. Raman spectrum of the isolated target resin **20a** (60 mW, 1064 nm), ṽ = 3057, 3000, 2932, 2859, 2804, 1662, 1600, 1440, 1407, 1336, 1301, 1222, 1161, 1129, 1093, 1032, 1002, 867, 660, 622 cm^{-1}.

3-Benzyl-3-polystyrylmethyl-1-(4-((E)-(4-dimethylaminophenyl) diazenyl)phenyl) triaz-1-ene (**20b**). Raman measurements were carried out according to method A and B. Raman spectrum of the isolated target resin **20b** (60 mW, 1064 nm), ṽ = 3053, 2954, 2927 2907, 2884, 2868, 2841, 1597, 1489, 1447, 1406, 1396, 1364, 1313, 1294, 1220, 1196, 1135, 1032, 1003, 739 cm^{-1}.

4-(-(4-(3-Benzyl-3-polystyrylmethyltriaz-1-en-1-yl)phenyl) diazenyl)-N,N-dimethylnaphthalen-1-amine (**20c**)
Raman measurement was carried out according to method A and B. Raman spectrum of the isolated target resin **20c** (60 mW, 1064 nm), ṽ = 3062, 2975, 2928, 2876, 1595, 1576, 1509, 1485, 1441, 1414, 1395, 1371, 1328, 1307, 1266, 1219, 1190, 1132, 1098, 1078, 1038, 1015, 1002, 926, 884, 836, 791, 691, 657, 624, 579, 494, 437, 384, 165, 124 cm^{-1}.

Diethyl (2-(4-(4-(2,2,2-trifluoro-1-(((polystyrylmethylsulfonyl) oxy)imino) ethyl)phenyl)-1H-1,2,3-triazol-1-yl)ethyl)phosphonate (**23**). Raman measurements were carried out according to methods A and B. Raman spectrum of the isolated target resin **23** (500 mW, 1064 nm), ṽ = 3058, 3000, 2976, 2912, 2241, 2203, 2185, 2158, 2139, 2076, 2061, 2044, 1616, 1559, 1450, 1184, 1157, 1033, 1003, 975, 799, 622, 231cm^{-1}.

3-Benzyl-3-polystyrylmethyl-1-(4-(phenylethynyl)phenyl)triaz-1-ene (**26**). Raman measurements were carried out according to methods A and B. Raman spectrum of the isolated target resin **26** (60 mW, 1064 nm), ṽ = 3060, 2923, 2855, **2215**, 1595, 1428, 1401 1224, 1163, 1137, 1031, 1002 cm^{-1}.

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Keywords: Raman spectroscopy • organic synthesis • polymer supports • in situ measurement • solid phase synthesis

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