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COMMUNICATION

Solid phase synthesis of selectively deuterated arenes†

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A novel access to deuterated and D_3CO-substituted arenes has been developed using immobilized triazenes as precursors. The linker system and the deuterating cleavage methodology could be shown to be compatible with various functional groups and are therefore suitable for the synthesis of derivatives only hardly available *via* comparable protocols.

Stable deuterated compounds are very important substances in analytics,[1] pharmacology,[2] material sciences,[3] and life sciences.[4] Deuterated compounds, physicochemically nearly identical to the non-deuterated ones, are used for NMR experiments and mechanistic studies,[5] neutron scattering,[6] and Raman spectroscopy,[7] reflecting the unique isotopic effects of deuterium.[8] The kinetic isotopic effect of deuterium[9] in particular is used for the synthesis of metabolically more stable active compounds yielding drugs with identical pharmacodynamic effects but different pharmacokinetics.[10] Recently, a high demand for partly and fully deuterated compounds was created for patent purposes; this is also an increasingly common business model for newly established companies.[11] Due to the high demand for these compounds, many high-yielding methods have been developed for their generation. The synthesis of deuterated arenes is mostly based on halogen–metal exchange reactions and subsequent quenching with heavy water.[12] Unfortunately, all effective methods suffer from harsh reaction conditions and low selectivities, tolerating only a small number of functional groups.

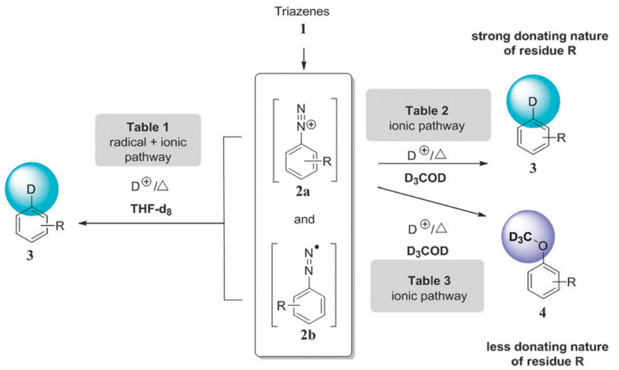
Beyond the introduction of a single deuterium, many attempts have been made to synthesize trideuterated substances *via* the formation of D_3CO-functionalities.[13] The synthesis of D_3CO-substituted arenes is important with regard to drug derivation for pharmacological[14] and analytical purposes related to drug abuse monitoring and quantitative detection of, for example, THC derivatives.[15]

The disadvantages of the existing protocols for deuterium or D_3CO-derivation such as harsh reaction conditions, low selectivities and the use of toxic reagents are manifold, and many attempts have been made to overcome them. Monodeuterated compounds have been isolated in good yields by replacement of diazonium groups through deuterium using thiophenol-d_1[16] or deuterated dimethylformamide in combination with $FeSO_4$.[17] As far as we know, there are no alternatives to the generation of arenes bearing a D_3CO-functionality which do not use MeI-d_3 or dimethylsulfate-d_6 as reagent.

In this communication we describe a new, mild and non-toxic alternative to known methods of D- and D_3CO-introduction *via* triazenes (Scheme 1). We focused on the development of advanced dediazoniation protocols which generally allow the conversion of molecules with various substitution patterns. The method developed herein has several advantages in comparison with those used until now: first we use only volatile solvents and reagents and work free of metal salts, thus rendering isolation and purification straightforward. Our reaction conditions do not require working under a controlled atmosphere and are well-designed for a solid phase chemistry strategy that should permit the generation of a library of small deuterated building blocks. In addition, this method is also suitable for solution phase chemistry.

Synthesis of monodeuterated arenes: all reactions were performed on triazenes in solution or on triazene-containing resins which are readily accessible *via* reaction of benzylamine resin with amines.[18] This well-established linker system is known to be easily cleavable through the addition of acid, giving the corresponding diazonium salts *in situ*. The resulting diazonium salts are thermally decomposed at 80 °C in THF-d_8 or D_3COD, yielding the deuterated target compounds in a one-pot synthesis without requiring isolation of the toxic and unstable diazonium salts.

All substances could be isolated without further aqueous workup after removal of the resin by filtration, evaporation of the solvent and column chromatography. Table 1 summarizes our



Scheme 1 Triazene decomposition and dediazoniation to the solvent-controlled formation of deuterium or CD_3O-substituted arenes **3** and **4**.

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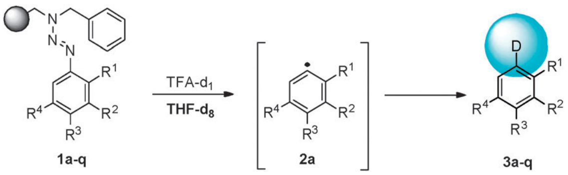
Table 1 Cleavage of monodeuterated arenes from triazene resins in THF-d_8



No	Resin	R^1	R^2	R^3	R^4	Yield [%]	*D* [%]
1	**1a**	OAr (OMe, *p*-Me)	H	H	H	61	95
2	**1b**	OAr (*o*-OEt)	H	H	H	>99	93
3	**1c**	OAr (*m*-CHO)	H	H	H	84	95[b]
4	**1d**	OAr (*m*-OMe)	H	H	H	>99	95
5	**1e**	OAr (*m*-^{i}Pr)	H	Br	H	81	96
6	**1f**	OAr (*m*-^{i}Pr)	H	Me	H	>99	94
7	**1g**	O-Biphenyl	H	Me	H	98	96
8	**1h**	O-Ph	H	H	H	66	95[b]
9	**1i**	O-Ph	H	H	Cl	56	95[b]
10	**1j**	OMe	H	NO_2	H	>99	91
11	**1k**	H	H	OPh	H	57 (60)[a]	96
12	**1l**	–CHCHCHCH–		Br	H	49	94
13	**1m**	H	H	Ar (*p*-OMe)	H	30	95
14	**1n**	F	H	Ar (*p*-OMe)	H	62	97
15	**1o**	H	H	–C≡C–Ph	H	57	91
16	**1p**	F	H	–C≡C–Ph	H	43	94
17	**1q**	H	H	–C≡C–Ar(*p*-OMe)	H	85	94

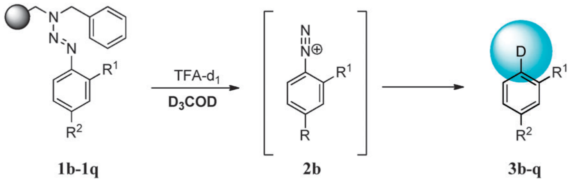
[a] Yields in brackets refer to syntheses on the mmol scale. [b] Rate of deuteration determined *via* NMR spectroscopy.

results giving monodeuterated substances after reaction in THF-d_8. The majority of the yields given therein were determined over two steps (one modification of on bead and deuterating cleavage) as the conversion on bead after a metal-involving coupling reaction is difficult to determine. Isolated yields over two steps are good to very good proving that the deuterating cleavage is a very effective method that can compete against known protocols.

The obtained yields of electron-rich and electron-deficient arenes were comparably high, which are in accordance with the supposed radical mechanism of the deuterating cleavage in THF (Scheme 1).[19] Reactions were frequently performed with *ortho*-immobilized diaryl ethers because the synthesis of this substance class on solid phases is well-established, and gives in most cases good conversions and yields. During our investigations of monodeuteration in different solvents, we observed that monodeuteration can also be achieved *via* conversion in deuterated methanol in cases when *ortho*-immobilized ethers are cleaved (entries 3 and 4, Table 2). Encouraged by these results, which are obviously a consequence of an electronic effect on the cleaved arenes, we could also achieve the effective deuteration of arenes in methanol-d_4 in the presence of TFA-d_1 for other substrates. Entries 1 and 2 (Table 2), which refer to alkyne-substituted arenes, gave excellent results, rendering the method a very effective alternative to the THF protocol (Table 1). The methanol approach becomes very attractive regarding the cost effectiveness of the reaction, especially upon increasing the scale (methanol-d_4 is cheaper than THF-d_8 and polystyrene based resins do not swell in methanol: less solvent is needed). The deuteration methodology was also performed on the mmol scale.

Synthesis of D_3CO-derivatives: the synthesis of D_3CO-substituted arenes was performed using some of the identical resin bound triazenes converted in the monodeuterating syntheses, as described in Table 1. The starting material and the cleavage procedure were the same, however, simply a change of the solvent to methanol-d_4 enabled the synthesis of D_3CO- rather than D-substituted products. Additionally, the D^+/H^+ source could now be used in its non-deuterated form. Table 3 summarizes the results achieved through addition of methanol-d_4 and TFA to triazene resins and reaction at 80 °C for 12 hours. As the reaction is presumed to follow an ionic pathway, the results depend on the electronic nature of the immobilized arenes. Arenes with electron-donating substituents often gave lower yields of, or could not be converted into, the corresponding D_3CO-derivatives. These substrates gave the monodeuterated compounds when reacted according to Table 3 (see also Table 2).

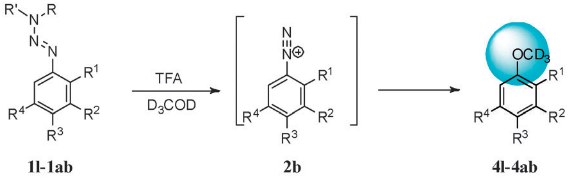
Table 2 Cleavage of monodeuterated arenes from triazene resins in methanol-d_4



No	Resin	R^1	R^2	Yield [%]	*D* [%]
1	**1o**	H	–C≡C–Ph	>99	93
2	**1q**	H	–C≡C–Ar(*p*-OMe)	>99	99
3	**1b**	OAr (*o*-OEt)	H	39	90
4	**1d**	OAr (*m*-OMe)	H	30	92

To our knowledge, the method described herein is the first allowing for the selective introduction of a D_3CO-group into arenes *via* conversion of triazenes, offering the possibility for the synthesis of D_3CO-modified molecules without the need of deuterated methyl iodide or dimethylsulfate-d_6. Due to the synthesis *via* dediazoniation, one D_3CO-group can be generated

Table 3 Generation of D_3CO-substituted arenes from triazene resins in CD_3OD



1l-1z : R = Bn, R' = polystyrenylmethyl
1aa/ab: R = R' = ${}^iPr$

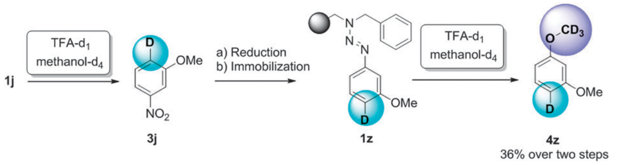
No	Resin	R^1	R^2	R^3	R^4	Yield [%]
1	**1l**	–CHCHCHCH–		Br	H	56
2	**1m**	H	H	Ar (*p*-OMe)	H	55
3	**1r**	H	H	Ph	H	71
4	**1s**	Ph	H	H	H	76
5	**1t**	H	CH_2OH	H	H	51
6	**1u**	H	OMe	H	H	52
7	**1v**	Me	Cl	H	H	36
8	**1w**	Me	H	H	CO_2Me	73 (82)[a]
9	**1x**	$COCH_3$	H	H	H	62
10	**1y**	H	I	Me	H	44
11	**1z**	H	OMe	D	H	36
12	**1aa**	H	H	Ph	H	79[b]
13	**1ab**	$CHCHCO_2{}^tBu$	H	H	H	80[b]

[a] Yields in brackets refer to syntheses in the mmol scale. [b] Syntheses in solution.

in the presence of existing methoxy groups, or of benzoic acids or alcohol functionalities without side reactions, which renders the method a highly attractive possibility for a selective labeling protocol. The D_3CO-generating cleavage protocol has been verified on the mmol scale as well, giving the target molecule **4w** (entry 8, Table 3) in a comparable yield. The D_3CO-introduction has been shown in solution as well. For this reason, we synthesized triazenes with the diisopropylamino backbone, furnishing target substances (**4aa** and **4ab**, entries 12 and 13, Table 3) in 79% and 80% yields, respectively.

To emphasize the scope of the deutero-dediazoniation protocols presented herein, we applied our methodology to the synthesis of arenes with a twofold deuterium-substitution. Resin **1j** was re-synthesized on the gram scale and subsequently reacted according to general procedure 8 (see ESI† GP8) to give deuterated nitroarene **3j**. After conversion into the corresponding amine and immobilization on benzylamino resin (to give **1z**), the dediazoniation could be applied again successfully. In this particular case, due to the absence of an *ortho*-ether functionality, the reaction yields over two steps the D_3CO-substituted compound **4z** in 36% yield (see Scheme 2).

The herein presented methods for the synthesis of compounds with deuterium- and D_3CO-substitution simplify the generation of deuterated compounds and offer a new effective, non-toxic, mild reaction pathway to those substrates. Initially developed with the small scale synthesis of deuterated building blocks for the formation of libraries in mind, the methodology proved to be readily scalable to a mmol scale, yielding the target substrates in high yields with a minimum of preparative effort. The methodology for monodeuteration in THF-d_8, including the cleavage procedure, is both high yielding and substituent-independent, allowing for the first time the selective introduction of deuterium in arenes in the presence of functionalities such as halogen substituents and carbonyl residues. By using methanol-d_4, the cost-effectiveness of the reaction can be improved in the case of electron-rich arenes. Starting with the same triazene linker system, we also developed a high-yielding method for the preparation of trideuterated compounds. Without precedent, the synthesis of D_3CO-bearing derivatives in the presence of carboxylic acids and alcohols was achieved independently of the use of toxic methylating agents. Lastly, we have demonstrated that a combination of the methods described herein can even be used for the synthesis of arenes displaying more than one deuterium substitution.



Scheme 2 Combination of protocols: synthesis of arenes with deuterium and OCD_3 substitution. (a) Pd/C, H_2, MeOH, rt, 12 h, (b) i. $C_5H_{11}ONO$, $BF_3{\cdot}Et_2O$, THF, −20 °C; ii. pyridine, MeCN, benzylamine resin, −20 °C–rt, 12 h.

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