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Solid supported fluoronitroaryl triazenes as immobilized and convertible Sanger reagents – synthesis and S_NAr reactions towards a novel preparation of 1-alkyl-5-nitro-1*H*-benzotriazoles†

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Synthesis of novel fluoronitroaryl triazenes in liquid phase and on solid support have been described; mild displacement of the fluoride ion with various nucleophiles provides access to substituted arenes which in turn can be cleaved to provide a unique access to 1-alkyl-5-nitro-1*H*-benzotriazole.

The nucleophilic displacement of activated haloarenes is an indispensable tool for the synthesis of highly substituted arenes. Fluoronitroarenes especially have served as excellent precursors in this transformation. The Sanger reagent (2,4-dinitrofluorobenzene) has been widely used because of its smooth reaction with amines at room temperature without activation,[1] however it is claimed to be possibly carcinogenic.

Fluoronitroarenes have also been immobilised on solid support using a carboxy linkage giving rise to the formation of heterocyclic structures.[2,3] Functionalization of the nitro group led after elaboration to the synthesis of arylamines, thioethers, oxazocines, and benzo annelated heterocycles such as benzothiazepin-4-ones, benzothiazocin-5-ones, benzodiazepin-2-ones, benzothiazin-3-ones quinoxalinones (benzopiperazinones), benzimidazoles, benzimidazolones, 2-thiobenzimidazoles, and 2-aminobenzimidazole. Especially 4-fluoro-3-nitrobenzoic acid and, less frequently, 2-fluoro-5-nitrobenzoic acid are suitable building blocks.

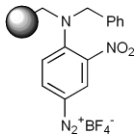
Recently, the triazene T1 linker has been introduced as a multifunctional anchor for arenes.[4,5] It has been shown that this linker could be converted into various functional groups upon cleavage. Moreover, the triazene group activates the arene by lowering the electron density of the core.[6]

Thus, it was appealing to combine the SNAr reaction with the flexibility of the diazonium chemistry. Therefore, an immobilized fluoronitrophenyl triazene would be an equivalent to the Sanger reagent.[1] First, the reactions were studied on a liquid phase model having a dibenzylamino core.

Starting from commercially available 4-fluoro-3-nitroaniline (**1**), diazotation and coupling to dibenzylamine produced the corresponding triazene **3** (Scheme 1). During the optimisation it was observed that excess of the amine rapidly reacts with the triazene **3** to give the *p*-dibenzylamino derivative **5** (Nu = NBn_2). The reaction of the diazonium ion **2** with exchange of the fluorine atom seemed to be slower because of starting from equimolar ratios of the starting materials; the non-substituted triazene was formed in 67%. The hydrolysis of diazotised 4-fluoro-3-nitroaniline was reported earlier to proceed under mild conditions.[7]

Similarly, the regioisomeric triazene **11** was synthesized from 2-fluoro-5-nitroaniline (**9**). In this case, a substantial lower reactivity towards nucleophiles was observed.

After these encouraging results, the reaction on solid support was examined. Therefore, benzylamino methyl polystyrene (Novabiochem or Polymers Labs, approx. 1 mmol g^{-1},1–2% crosslinked with divinylbenzene) was treated with the fluoronitrobenzene diazonium salt **10** to give the triazene **12**. At this point, it was crucial to avoid hydroxylic solvent as *e.g.* methanol in the washing step since the fluorotriazene reacts with this solvent. Acetone has been found to be a good substitute for methanol. According to ^{19}F gel phase NMR spectroscopy, IR and elemental analysis, the loading efficiency was excellent.



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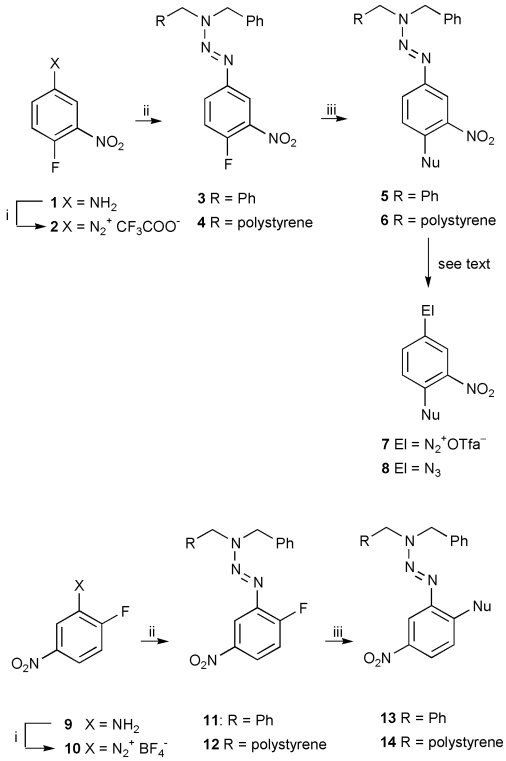
During the attempts to prepare the analogous resin **4**, the temperature stable diazonium resin **15** (*cf* ref. 8) was formed in nearly quantitative yield (IR stretch at 2016 cm^{-1}). However, after variation of the coupling procedure and reagents, the formation of diazonium salt **15** could be suppressed using trifluoroacetic acid. A slight drawback of this method is the occurrence of partial substitution of the fluorine atom by



Scheme 1 *Reagents and conditions*: i, BF_3OEt_2, isoamylONO; ii, RCH_2NHBn, THF; iii, NuH, pyridine, 60 °C, 48–90 h.

† Electronic supplementary information (ESI) available: experimental procedures. See http://www.rsc.org/suppdata/cc/b2/b201489k/

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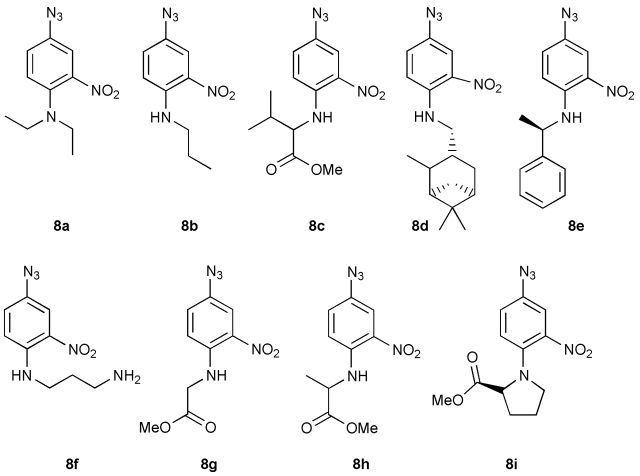
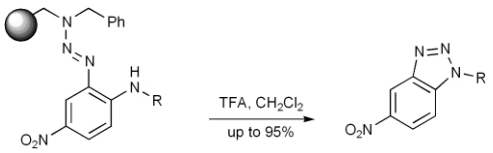


Fig. 1 Arylazides prepared.

trifluoroacetate, which leads to the formation of the appropriate phenol (after hydrolysis). The nucleophilic substitutions on resin were examined with primary and secondary amines in the presence of caesium fluoride and caesium carbonate at 60 °C in DMF and were found to proceed in good conversion within 48–90 h to yield the resins **6**. Cleavage of the resins **6** with trifluoroacetic acid give the diazonium salts **7**.[9] Alternatively, cleavage with TFA–trimethylsilyl azide in dichloromethane at room temperature furnished aryl azides **8** (Fig. 1) in excellent purity after 5 min of reaction time.[10]

Although the preparation of 1-alkyl and aryl benzotriazoles from symmetrical and unsymmetrical diamines by diazotation in moderate to good yields is well-known,[11] a synthesis starting from triazenes has not been reported to our knowledge. Benzotriazoles are important intermediates, protecting groups and final products in Organic Synthesis.[12] Furthermore, benzotriazoles are indispensable tools for the synthesis of various functional groups. Various 1-alkyl benzotriazoles are biologically active and show nanomolar binding affinities to various proteins although this structural unit could not be found in nature.[13] The antiemetic and neuroleptic Alizapride (Vergentan®) is a 3-unsubstitited 3*H*-benzotriazole and used for the treatment of side effects in chemotherapy caused by Cisplatin.[14] Recently, benzotriazoles have served as linkers and auxiliaries in solid phase synthesis.[15] Therefore, we investigated the conversion of the polymer-bound fluoronitroarenes **14** to 1-alkyl benzotriazoles. To our delight, the cleavage of triazene



14a: R = Allyl
14b: R = *c*Pr
14c: R = *c*Pent
14d: R = *p*-MeOC$_6$H$_4$CH$_2$

16a
16b
16c
16d

Scheme 2 Synthesis of benzotriazoles **16**.

bound anilines **14** with trifluoroacetic acid in dichloromethane proceeded smoothly at room temperature within minutes to give the desired 1-alkyl benzotriazoles **16** in excellent yield and purities (Scheme 2).

In conclusion, we developed a new synthesis of substituted arenes suitable for the triazene T1 linker and a novel synthesis of 1-alkyl-5-nitro-1*H*-benzotriazole suitable for automated synthesis.

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