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SELECTIVE PROTECTION OF 5-AMINOBENZOTRIAZOLE FOR CONTROLLED REACTION AT THE PRIMARY AMINE

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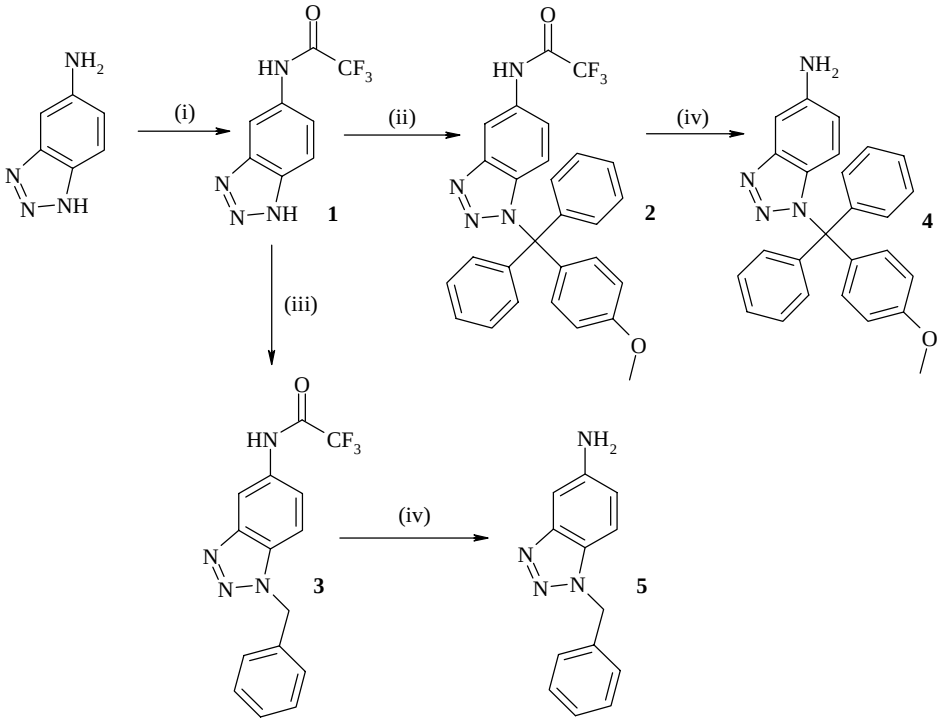
Abstract- The selective protection of the triazole function of 5-aminobenzotriazole is reported. Two different protecting groups were used to prevent side reactions through the triazole amine acting as a leaving group when 5-aminobenzotriazole was used as a nucleophile. This allowed the addition of aminobenzotriazole to two target molecules to impart metal complexing properties to the new species.

Benzotriazole is a commonly used metal complexing agent and has found use as an anti-tarnish agent for copper and silver by forming surface monolayers to prevent oxidation.[1] Recently we have made use of benzotriazole to attach oligonucleotides to metal surfaces as part of our study into the surface enhanced resonance Raman scattering (SERRS) of synthetic oligonucleotides.[2,3] This produces an essentially irreversible bond to metal surfaces and is known to displace other surface species.[2] Benzotriazole chemistry is complex and several excellent reviews cover most of the chemistry often associated with benzotriazole.[4,5] One of the most utilised chemical properties of benzotriazole is the ability to act as an excellent leaving group with it often being referred to as a 'poor halide'. When trying to add benzotriazole to other molecules to impart some of the benzotriazole properties to the target this reactivity can often lead to considerable problems. There are numerous benzotriazole derivatives that can be used to react with specific functional groups such as 5-chlorobenzotriazole or benzotriazole-5-carboxylic acid but one of the most readily available nucleophilic derivatives is 5-aminobenzotriazole.[6]

As part of our on going research into surface chemistry we wanted to produce fluorophores with the ability to form a surface layer on a metal. There are a large number of commercially available fluorophores but only a limited number with a reactive functionality directly on the fluorescent ring system. The two fluorophores chosen for reaction were dansyl chloride and rhodamine B sulfonyl

chloride. Both fluorophores have sulfonyl chloride groups that can react with primary amines to give a stable sulfonamide linkage. Initially, reaction of the sulfonyl chlorides with 5-aminobenzotriazole under a number of different conditions was attempted. This constantly gave rise to complex mixtures that were difficult to purify. Thus, it was decided that a protected aminobenzotriazole moiety was necessary for this and similar reactions.



Scheme 1 (i) $(CF_3CO)_2O$, DMF, 85 % (ii) MMTrCl, Py, DMAP, 57 % (iii) BnBr, toluene, Et_3N, 52 % (iv) K_2CO_3, MeOH, Δ, 68 %

The first step in the synthesis of the protected 5-aminobenzotriazole (Scheme 1) was reaction with excess trifluoroacetic acid in DMF to produce the trifluroacetamide selectively on the primary amine (**1)**. (If a hindered base is added then additional trifluoroacetylation occurs on the triazole proton. This is due to the trifluoroacetic acid produced being neutralised by the base not hydrolysing the triazole trifluoroacetamide.) This leaves the triazole function free and the amine protected with a base labile protecting group. The next stage was choice of a suitable protecting group for the triazole function. As a base labile group was being used on the primary amine, an acid labile group was picked for this task. Two groups were examined, the first being monomethoxytrityl chloride which was added to the protected aminobenzotriazole in pyridine with a catalytic amount of DMAP. The second group examined was the benzyl group which was added by use of benzyl bromide in toluene with triethylamine. Addition of both groups produced regioisomers due to the tautomeric nature of the triazole function. Subsequent reactions used the mixture of isomers without separation. The major isomer is shown in the Schemes. To produce the free amines, the fully protected benzotriazole derivatives were heated with potassium carbonate in methanol to cleave the trifluoracetamide. The primary amine was then free to react selectively with

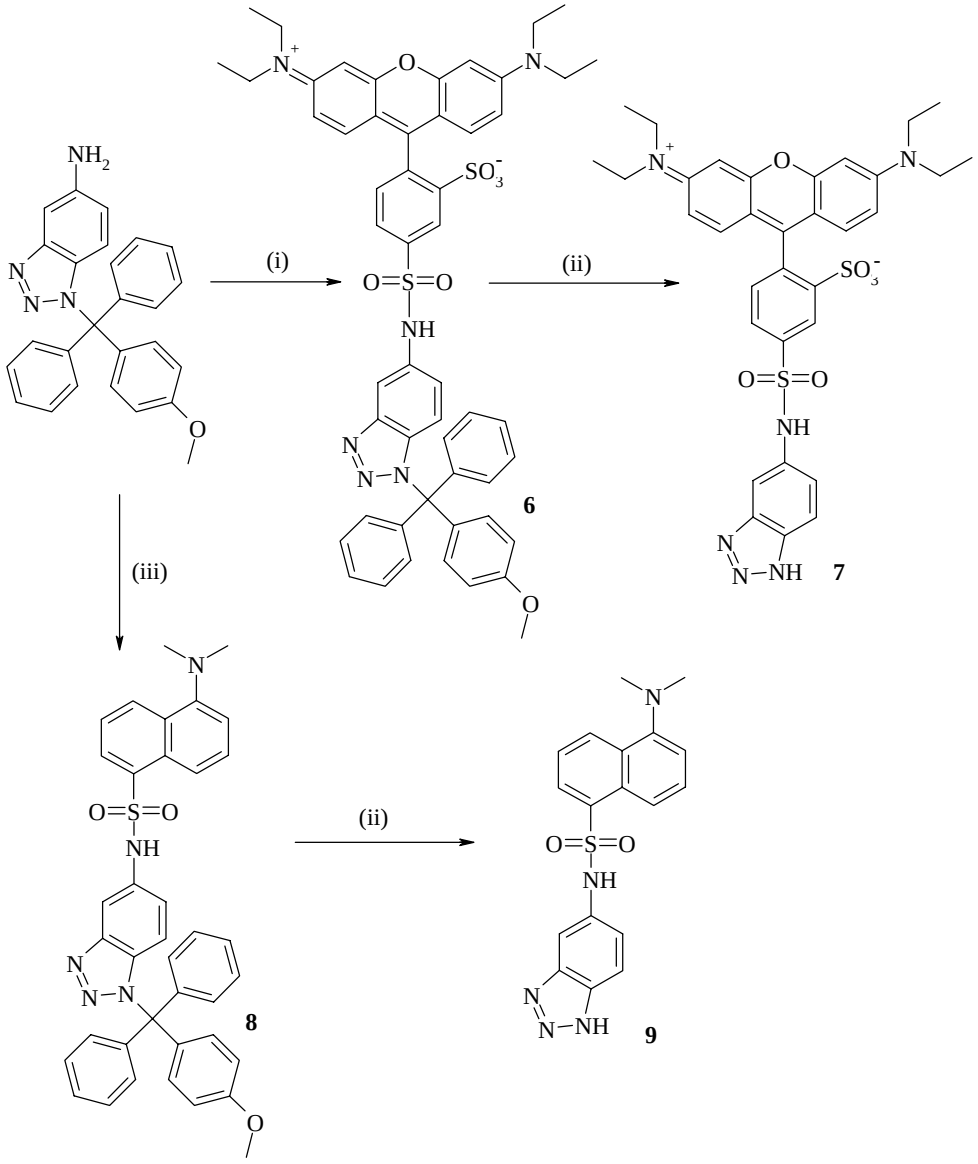
reactive functionalities such as the sulfonyl chlorides under standard basic conditions. A one-pot synthesis of the monomethoxytritylated aminobenzotriazole was also attempted and gave a 46 % yield compared to the three-step procedure which gave a 33 % yield. Both routes required one column chromatography purification.

The base stability of the triazole-protected species (**4**) and (**5**) was examined to determine the extent of basic conditions permissible for further reaction. The following bases were used: concentrated ammonia, piperidine, DBU and sodium methoxide. Both compounds (**4**) and (**5**) were stable at room temperature for 24 h to all of the bases, however, when heated the monomethoxytritylated aminobenzotriazole was converted back to 5-aminobenzotriazole after 30 min by all of the bases. In contrast the benzylated aminobenzotriazole (**5**) was stable when heated with all of the bases. In addition to using acid labile protecting groups two base labile protecting groups were examined on the triazole ring. The pivaloyl and fluorenylmethyl groups were added to the trifluoroacetamide protected aminobenzotriazole (**1**) and their stability to potassium carbonate and heat tested. Both the hindered amide and carbamate were cleaved by heating in potassium carbonate indicating their unsuitability as protecting groups for aminobenzotriazole. Thus, the acid labile groups were chosen for further reactions.

The conditions for removal of the monomethoxytrityl and benzyl groups were investigated and it was found that TFA cleaved both protecting groups cleanly in 15 min to return the aminobenzotriazole. In the case of the monomethoxytrityl an excess of pyrrole was also added as a scavenger,[7] to trap the tertiary cation formed which can react with the liberated amine again.

In order to demonstrate the usefulness of these compounds the monomethoxytritylated aminobenzotriazole was coupled to rhodamine B sulfonyl chloride and dansyl chloride in pyridine with a catalytic amount of DMAP in a repetition of the previous experiments with the unprotected 5-aminobenzotriazole. (Scheme 2) The rhodamine derivative (**6**) was isolated by column chromatography in 88 % yield before removal of the monomethoxytrityl group using TFA and pyrrole gave the desired compound (**7**) in 89 % after purification by chromatography. The reaction with dansyl chloride gave the protected species (**8**) in 64 % yield after a basic extraction and the desired compound (**9**) was produced after removal of the protecting group.

In conclusion, this communication demonstrates how to selectively protect 5-aminobenzotriazole to ensure a clean reaction at the primary amine group. The protecting groups have been chosen for use under basic conditions which favour the types of reaction normally used with primary amines. Two fluorescent compounds that had been difficult to synthesis previously from 5-aminobenzotriazole were prepared in good yield. The use of these protected benzotriazole compounds will allow the synthesis of a range of compounds for use in the study of metal ions or metal surfaces.



Scheme 2 (i) RhodB SO_2Cl, Py, DMAP, 88 % (ii) TFA, pyrrole, DCM, 89% (iii) Dansyl Cl, Py, DMAP, 64 %

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