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Efficient solid phase synthesis of benzo[1,2,3]thiadiazoles and related structures†

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The first solid-phase synthesis of benzo[1,2,3]thiadiazoles was achieved by starting from resin bound *ortho* bromo or iodo triazenes and using a functionalisation on cleavage.

1,2,3-Thiadiazoles are heterocycles of great practical and theoretical interest.[1] Especially derivatives of benzo[1,2,3]thiadiazoles are important in industry and agriculture.[2] They have been recognised as the first synthetic chemical plant activators, which can induce disease resistance in plants, the so-called systemic acquired resistance (SAR).[3]

The *S*-methyl ester of benzo[1,2,3]thiadiazole-7-thiocarboxylic acid (Acibenzolar-*S*-methylester) (Fig. 1) was introduced as Bion® or Actigard®, respectively, as the first commercial product of this type by Novartis.[4] It has been shown that Acibenzolar-*S*-methylester induces disease resistance in wheat,[5] tobacco,[6] Arabidopsis,[7] melons[8] and maize.[9] It can be used as a substitute for antibacterial and antiviral compounds as well as for fungicides. Brisset *et al.*[10] have found that Acibenzolar-*S*-methylester induces the accumulation of defence-related enzymes in apples and thereby protects them efficiently against fire blight. Bion® is commercially used as a pesticide on wheat, radish, lettuce and spinach.[11] While there are synthetical approaches towards benzo[1,2,3]thiadiazoles in solution, mainly *via* the Wolff method and the Hurd–Mori reaction,[12] they mainly suffer from their lack of compatibility with functional groups as well as poor availability of starting materials. Furthermore, the synthesis of benzo[1,2,3]thiadiazoles on solid support has, to our knowledge, not been achieved so far.

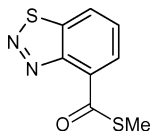


Fig. 1 Structure of Acibenzolar-*S*-methylester (Bion®).

We herein report the first synthesis of a variety of benzo[1,2,3]-thiadiazoles and related structures on solid support, employing two different, synergetic methods: An anionic approach, *via* a halide metal exchange[13] and a cross-coupling approach, *via* an innovative palladium catalysed C–S bond forming reaction.[14]

We first became interested in the synthesis of benzo[1,2,3]-thiadiazoles during our synthetic studies of the triazene linker system (T1).[15] By then, we realised that sulfur electrophiles could easily be reacted with resin-bound haloarenes, using *n*-butyllithium or a palladium-based protocol developed in our group.[16] When cleaving the arenethiol resins, the resulting diazonium compounds readily underwent electrophilic cyclisation yielding benzothiadiazoles.

By diazotation of the anilines **1a–i** (Fig. 2) with *tert*-butyl nitrite and subsequent coupling to the piperazine resin **2**,

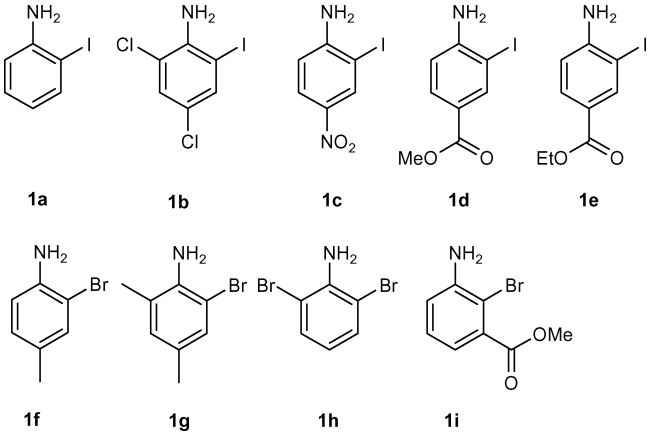
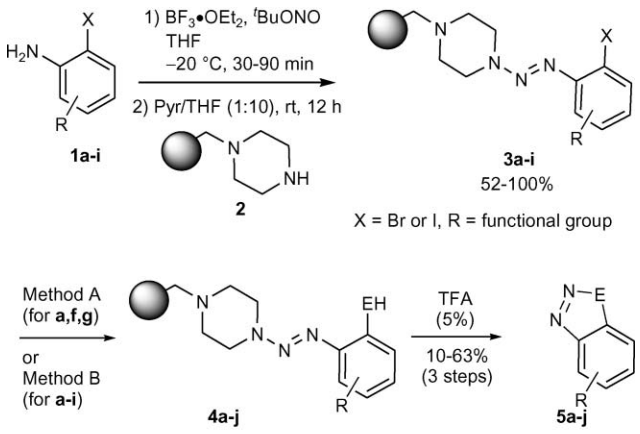


Fig. 2 Bromo- and iodo-anilines used for heterocycle syntheses.

triazene bromo- or iodo aryl resins **3a–i** were prepared on a multigram scale (1–10 g) in medium (52%) to full conversion.

The resulting triazene aryl halide resins **3a–i** could then be converted to the corresponding triazene thiol or selenol resins by two alternative methods. Method A (Scheme 1) starts with a halide–lithium exchange with *n*-BuLi and TMEDA, followed by treatment with elemental sulfur or elemental selenium.



Scheme 1 Synthesis of benzo[1,2,3]thia- and selenadiazoles. Method A: 1) *n*-BuLi, TMEDA, THF, −40 °C, 1 h; 2) S_8, THF, rt (E = S) or grey Selen (E = Se); Method B: 1) TIPSSH, Cs_2CO_3, 15 mol% $Pd(OAc)_2$, PPh_3, toluene, 85 °C, 16 h; 2) TBAF, THF, rt, 2 h.

Method B (Scheme 1) uses a palladium-catalysed cross-coupling reaction protocol with triisopropylsilylthiol (TIPSSH), followed by deprotection with tetrabutylammonium fluoride (TBAF) in THF. The results are summarised in Table 1.

Cleavage from the resin with diluted trifluoroacetic acid resulted spontaneously in the desired cyclisation reaction,

† Electronic supplementary information (ESI) available: Experimental details and data. See http://www.rsc.org/suppdata/ob/b5/b504900h/

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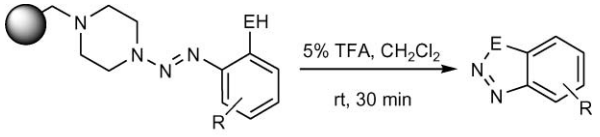
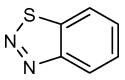
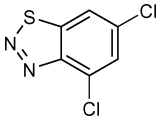
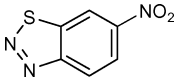
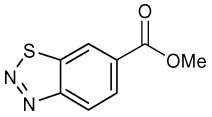
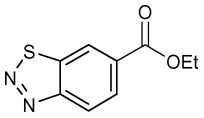
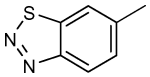
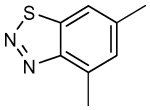
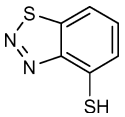
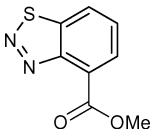
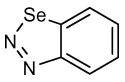
Table 1 Synthesis of benzo[1,2,3]thiadiazoles and benzo[1,2,3]selenadiazole



4a-j **5a-j**

E = S or Se, R = functional group

Entry	Product	Yield[a]
1		53%[b] 62%[c]
2		10%[c]
3		37%[c]
4		34%[c]
5		41%[c]
6		45%[b] 42%[c]
7		56%[b]
8		Traces[b] Traces[c]
9		15%[c]
10		63%[b]

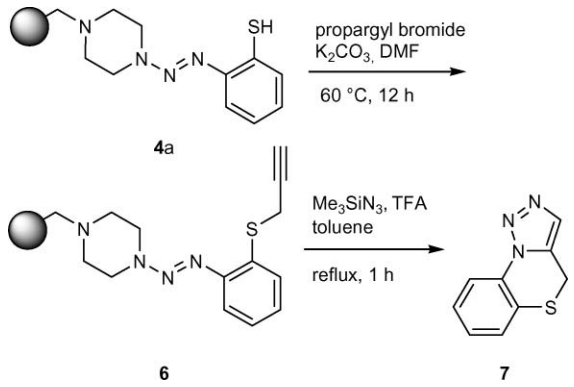
[a] Isolated yield after chromatography. [b] Lithiation protocol: 1) 1.0 g resin, TMEDA (5.4 mmol), *n*-BuLi (5.4 mmol) in THF under argon at −40 °C to rt, then S_8. 2) TFA in CH_2Cl_2 at rt. [c] Palladium-catalysed protocol: 1) 1.0 g resin, $Pd(OAc)_2$ (0.15 mmol), PPh_3 (0.60 mmol), Cs_2CO_3 (4.0 mmol), TIPSSH (2.5 mmol) at 85 °C in toluene under argon. 2) TBAF (2.5 mmol) in THF at rt. 3) TFA in CH_2Cl_2 at rt.

yielding benzo[1,2,3]thiadiazoles in good yields. Both, *ortho*-bromo and *ortho*-iodo anilines are excellent substrates for the synthesis of benzo[1,2,3]thiadiazoles. Both electron rich (entry 6 and 7) as well as electron poor (entry 2, 3, 4, 5 and 9) haloanilines achieved good results. Both methodologies are equally effective for unsubstituted and methyl substituted *ortho*-bromo and *ortho*-iodo anilines giving approximately the same results (entries 1 and 6). While the lithiation protocol failed for anilines bearing functional groups such as nitro (entry 3) and ester groups (entry 4), we were delighted to find that the palladium-catalysed methodology succeeded in converting these more demanding substrates into the desired products in good yields and purities. Even the sterically hindered Acibenzolar-*O*-methylester, with two substituents in the *ortho*-position could be synthesised in only slightly lower yields (entry 9). This conversion gives combinatorial access towards benzo[1,2,3]thiadiazole-7-carboxyclic acid derivatives, as a substance class of chemical plant activators like Bion®.

Considering our success with benzo[1,2,3]thiadiazoles, we employed our strategy in the synthesis of benzo[1,2,3]selenadiazole, which could be synthesised by the lithiation protocol in a good yield (63%) and purity. Benzo[1,2,3]selenadiazoles are only scarcely found in literature[17] and show antioxidative as well as antibacterial activities.[18]

While the advantages of the first methodology are the lower costs and the ecological harmlessness of the waste, the second methodology performs better as regards to functional group tolerance and gives rise to a potential combinatorial approach towards benzo[1,2,3]thiadiazoles.

With these results at hand, we envisioned that this strategy could also give access to other heterocyclic systems, simply by reacting the thiol resins with various electrophiles followed by cleavage (Scheme 2).



Scheme 2 Synthesis of 4*H*-[1,2,3]-triazolo[5,1-*c*][1,4]benzothiazine.

Therefore, thiol resin **4a** was reacted with propargyl bromide to give thiopropargylether resin **6**. In order to apply our functionalisation on cleavage strategy, the diazonium compound resulting from cleavage of **6** was converted into the corresponding aryl azide, a method which has been used previously.[19] On heating, this azide underwent [3 + 2]-cycloaddition to yield 4*H*-[1,2,3]-triazolo[5,1-*c*][1,4]benzothiazine in 14% overall yield (4 steps).[20] A library access to this class of compounds by Sonogashira coupling of thiopropargylether resins is currently being performed in our laboratory.

In summary, we have accomplished the first solid phase synthesis of benzo[1,2,3]thiadiazoles. The T1-triazene linker system was used for a functionalisation on cleavage. By employing two synergetic methodologies, we were able to synthesise a wide range of substituted benzo[1,2,3]thiadiazoles. Among these, Acibenzolar-*O*-methylester possesses a prominent position, being a precursor for a class of chemical plant activators like Bion®. Furthermore we were able to realise the synthesis of more complex heterocycles like 4*H*-[1,2,3]-triazolo[5,1-*c*][1,4]benzothiazine.

Acknowledgements

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