Synthesis and reactions of benzotriazolyl-substituted spiro[cyclohexane-1,2′-2′*H*-imidazo[4,5-*b*]pyridine]

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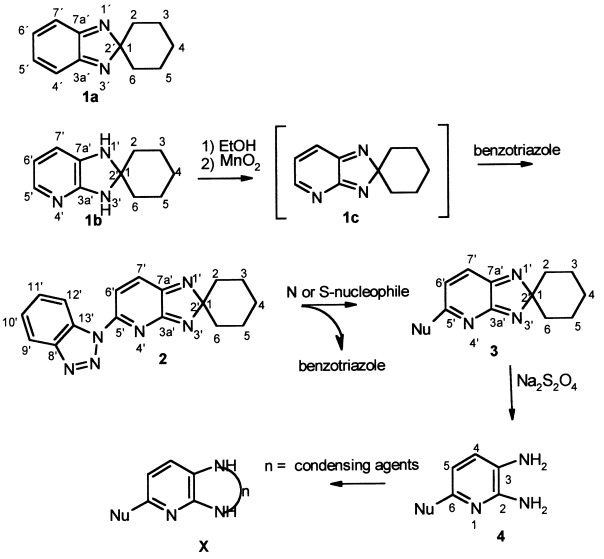
The introduction of N and S-nucleophiles into the 2*H*-4-azabenzimidazole system using the 1*H*-benzotriazole ring as a synthetic auxiliary, and also the syntheses of novel pentacyclic ring systems by application of the Graebe-Ullmann method, are described.

Keywords: nucleophilic substitution, spiro compounds, benzotriazoles, fused imidazoles, fused pyridines

Benzotriazole, a good leaving group, can be introduced into spiro[cyclohexane-1,2′-2′*H*-imidazo[4,5-*b*]pyridine] (2,3-dihydrospiro[2*H*-4-azabenzimidazole-2,1′-cyclohexane][†]) **1c** to give compound **2** and then exchanged by a series of N- or S-nucleophiles. The new N- and S-substituted products **(3)** possess considerable synthetic potential for preparing new heterocycles **(X)** of pharmaceutical interest by reductive hydrolysis followed by reacting the generated 2,3-diaminopyridine **(4)** with suitable reagents.[2-4] (Scheme 1) For instance, 5′-(benzotriazol-1-yl)-spiro[cyclohexane-1,2′-2′*H*-imidazo[4,5-*b*]pyridine] **2** is readily obtained by reaction of spiro[cyclohexane-1,2′(3′*H*)-1′*H*-imidazo[4,5-*b*]pyridine] **1b**[1] with 1*H*-benzotriazole in the presence of an excess of MnO_2 in tetrahydrofuran. The first step of the reaction is the oxidation of **1b** to give the highly reactive, non-isolable spiro[cyclohexane-1,2′-2′*H*-imidazo[4,5-*b*]pyridine] **1c**, which shows a structural relationship with spiro[2*H*-benzimidazole-2,1′-cyclohexane] **1a**,[5] a stable quinonediimine. Intermediate **1c** reacts immediately with the added benzotriazole to give compound **2** by Michael addition followed by oxidation.[6] Using the benzotriazole leaving group[7] the introduction of N- or S-nucleophiles into the 4-aza-compound is easily carried out to give a series of substituted spiro[cyclohexane-1,2′-2′*H*-imidazo[4,5-*b*]pyridines] or spiro[cyclohexane-1,2′(3′*H*)-1′*H*-imidazo[4,5-*b*]pyridines] as outlined in Schemes 2 and 3.

The benzotriazole function did not in fact prove to be an easy leaving group. Substitution was attempted with the following N-nucleophiles: ethyl 4-aminobenzoate, 2-(dimethylamino)ethyl 4-butylaminobenzoate, phenylhydrazine, pyridin-2-ylhydrazine, 4-amino-5-fluoro-1*H*-pyrimidin-2-one, isonicotinic hydrazide, 2-amino-3-(4-hydroxyphenyl)propionic acid hydrazide (tyrosine hydrazide), 4-amino-1*H*-pyrimidin-2-one, 7*H*-purin-6-ylamine (adenine) and piperidine. Only compounds **5, 6, 7, 8** and **11** could be realised with the application of this synthetic strategy (Scheme 2). The preparative significance of these compounds lies in their reductive ring-opening by sodium dithionite to give 2,3-diaminopyridines of type **4** (Scheme 1). In other cases either the benzotriazole residue was retained, the nucleophile entering the 7-position of the azabenzimidazole ring (with or without reduction of the imidazole ring) or the nucleophile entered the 7-position as well as displacing the benzimidazole, to form a disubstituted product.



Scheme 1 Formation and potential applications of the benzotriazolyl azabenzimidazole **(2).**

The following sulfur nucleophiles were also reacted with compound **2:** benzenethiol, pyridine-2-thione, pyrimidine-2-thione, 9-ribosylpurine-6-thione. In all cases the benzotriazole moiety was retained, and the sulfur substituent entered the 7-position, usually with reduction of the imidazole ring. These reactions are illustrated in Scheme 3.

Finally, by thermolysis of the benzotriazolyl compounds **2** and **21** in refluxing toluene in the presence of Hünig's base, a Graebe-Ullman type cyclisation occurred,[8] forming the fused benzimidazole derivatives **20** and **22**. The compound **21** was easily obtained from 1,3-dihydrospiro[2*H*-4-azabenzimidazole 2,1′-cyclohexane] **1b** by reacting with four times excess of benzotriazole in the presence of five moles of MnO_2.

Techniques used: IR, ^1H and ^{13}C NMR, MS

References: 8

Schemes: 4

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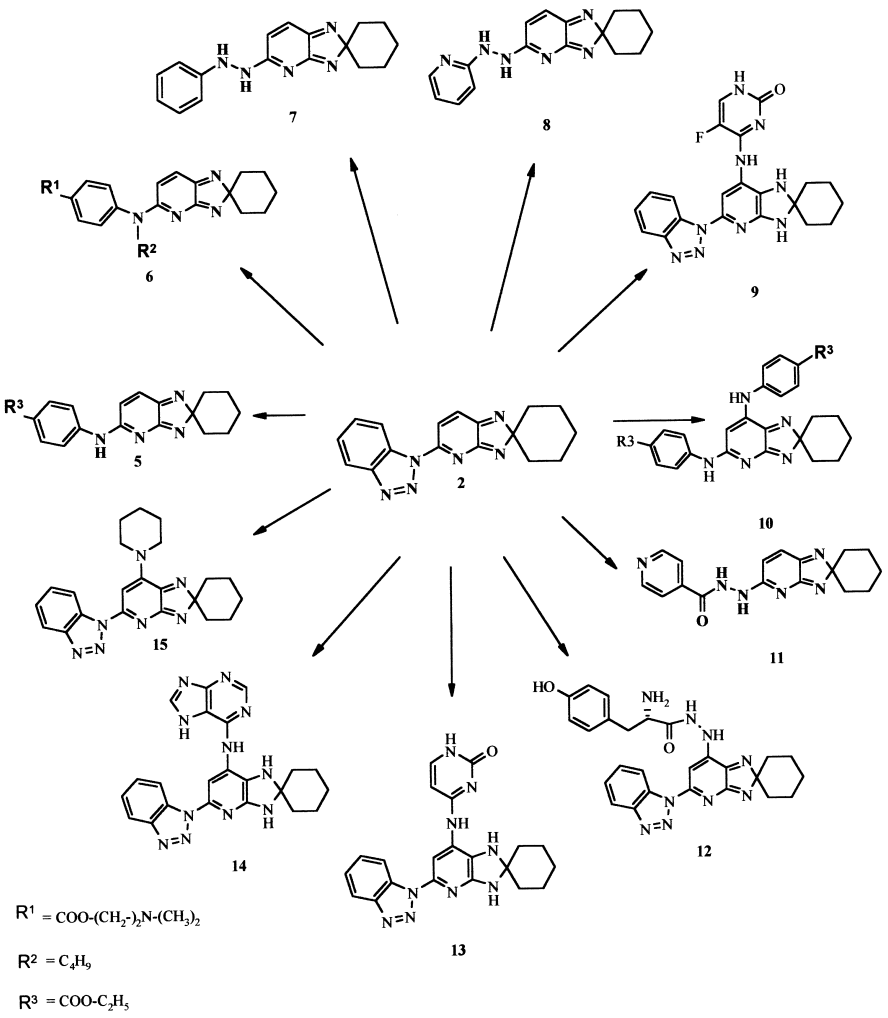
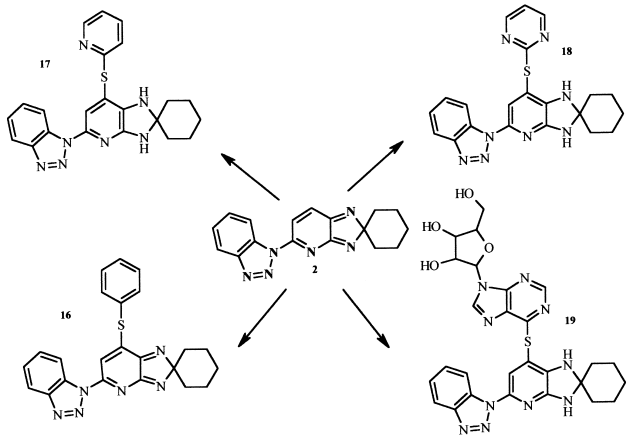
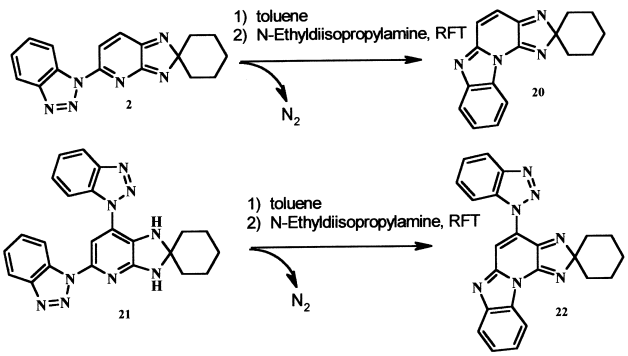
[†] Although it is not encouraged by the IUPAC rules, this style of nomenclature (aza-substitution of a heterocyclic system) is convenient to use in 'colloquial' fashion here.



Scheme 2 Reactions of compound **2** with N-nucleophiles.



Scheme 3 Reactions of compound **2** with S-nucleophiles.



Scheme 4 Thermolysis of benzotriazolyl-imidazo[4,5-*b*]pyridines.

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