PAPER

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Studies on the preparation of aminobipyridines and bipyridine sultams *via* an intramolecular free radical pathway†

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A variety of aminated bipyridines and bipyridine sultams are prepared by intramolecular radical [1,5]-*ipso* and [1,6]-*ortho* substitutions, using a sulfonamide as a linker to connect the pyridyl radical to the pyridine under attack. For the cases studied, different regiochemistries are observed depending on the initial position of the sulfonamide linker.

Introduction

Intramolecular aryl and heteroaryl radical addition to arenes represents a valuable and straightforward pathway to access biaryls and heterocyclic aryl derivatives. However, although this radical process has been widely studied in these areas,[1a–h] the preparation of an important class of bisheteroaryls, namely bipyridines, has received little attention.

Bipyridines are important scaffolds in many natural alkaloids and synthetic derivatives with a wide range of pharmacological activities (Fig. 1).[2a–g] In addition, they are widely used as ligands in organometallic chemistry and are important cores in novel polymeric electro-transporting materials and organic solar cells, amongst others.[3a–d] Moreover, although considerable attention has been devoted to the synthesis, study and characterization of dibenzosultams,[4a–j] no references have been found for the corresponding bipyridine derivatives.

As part of a research program devoted to studying the bis(hetero)arylation process, *via* a radical pathway, in the absence of transition metals, we have previously described a new preparation of the bisheterobiaryl sultam **1**, which contains a β-carboline core. The behavior of the starting pyridine sulfonamide **2** was studied under different conditions and only the bisheteroaryl sultam **1** was detected under all conditions.[5]

In order to study this cyclization in other related and simpler systems, and to shed some light on this finding, herein we report our studies of radical intramolecular bisheteroarylations

in the presence of tris(trimethylsilyl)silane and azobisisobutyronitrile (TTMSS/AIBN), using sulfonamide **3**, which is easy to prepare, as a linker to connect the pyridyl radical to the pyridine under attack, to give bipyridines **4** and/or bipyridine sultams **5**, depending on the initial substitution pattern (Scheme 1).

Results and discussion

Our work started with the preparation of sulfonamides **3**, as starting material for the radical cyclization process. According to Motherwell,[1d,6a,b] Togo[7] and others,[8] and taking into consideration our previous work,[9] it has been shown that the presence of the free NH can negatively affect the radical arylation reaction by facilitating reduction of the radical generated. In addition, the corresponding group in an *N*-alkylsulfonamide increases
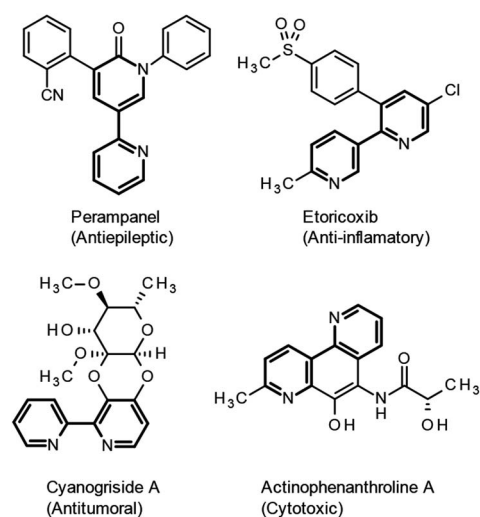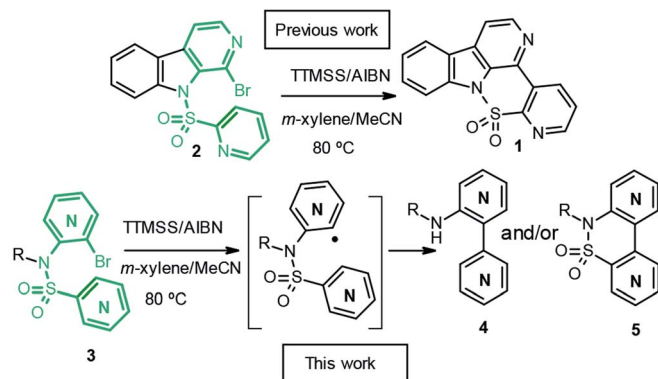
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Fig. 1 Significant bioactive bipyridines compounds.

Scheme 1 Background and objectives of this work.

Scheme 2 Synthesis of **8a–c**.

the stiffness of the sulfonamide bond with respect to a free NH, thus meaning that the *cis* conformation (**I** *versus* **II**, Fig. 2) turns out to be the most suitable for radical cyclization as the radical and the heteroaryl are closest to each other in space. In contrast, although a methyl group is most commonly used for this purpose, it is difficult to remove subsequently, therefore in addition to carrying out our experiments with a methyl group as substituent, we also used MOM (methoxymethyl), which is suitable for protecting sulfonamides but not amines.[10] Initial experiments were conducted with pyridine 2-sulfonyl chloride (**6b**)[11] (X = CH, Y = N, Scheme 2) and 2-bromo-3-aminopyridine (**7a**; Z = N, W = CH, Scheme 2), in refluxing Et$_3$N/CH$_2$Cl$_2$, although only a 34% yield of the desired compound **8c** was obtained (Method A).

Even worse results were obtained with the same starting products when using NaH as the base in refluxing MeCN or DMF (Method B).

The best results for the formation of sulfonamides **8a–c**, which contain a 2- or 3-aminopyridine core and a sulfonic acid residue formed from the chlorides of 3-[12] or 2-sulfonylpyridine **6**, were obtained by addition of 2 equiv. of pyridine sulfonyl chloride to a solution of 1 equiv. of amine in pyridine and stirring the mixture at 80 °C for 5 h (Method C).[13]
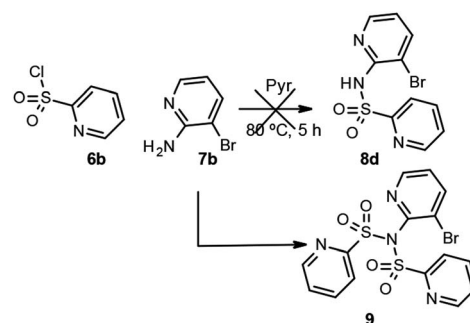
However, when the same method was applied for the formation of sulfonamide **8d**, using pyridine 2-sulfonyl chloride **6b** and the 2-aminopyridine **7b** as starting products, the desired product was not obtained and the main product was the double sulfonylation derivative **9** (Scheme 3). Product **9** is likely to be obtained as a consequence of the acidity of the NH of the sulfonamide in product **8d**. Thus, once **8d** has formed, and under the basic conditions of the reaction, the NH group deprotonates to give the conjugated base of acid **III** with additional resonance forms **IV** and **V**, in which the negative charge is
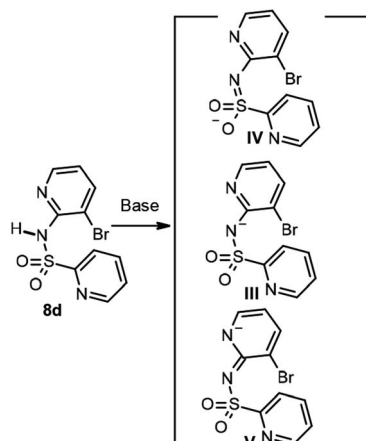
delocalized onto the sulfone group and the endocyclic nitrogen, respectively (Scheme 4).
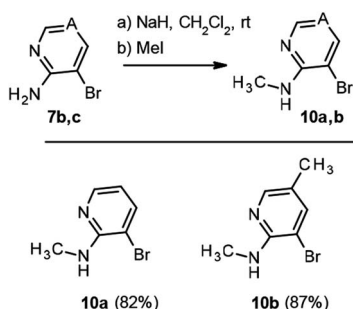
As this conjugated base is acylated again, the only detectable product is **9** (Scheme 3). In view of this finding, and in order to avoid formation of the double sulfonylation product **9**, the reaction between pyridine 2-sulfonyl chloride (**6b**) and the corresponding *N*-methyl-3-bromo-2-aminopyridines **10a,b** (Scheme 5), prepared by methods previously described in the literature,[14a,b] was considered as an alternative for the synthesis of pyridines **3d** and **3e**. In addition **3ba** was obtained from the methylated aminopyridine **10a**. Again, the sulfonylation reaction was carried out with **10a** and **10b** using Method C, for all cases, giving the corresponding sulfonamides **3ba**, **3d** and **3e** in good yields (Scheme 6). *N*-Alkylation of sulfonamides **8a–c** was carried out by addition of 1.1 equiv. of sodium hydride to a solution of 1 equiv. of sulfonamides in DMF and subsequent treatment with 1.1 equiv. of methyl iodide or methoxymethyl chloride. Scheme 6 shows our results in this process for *N*-alkyl sulfonamides **3aa**, **3ab**, **3bb**, **3ca** and **3cb**, as well as the result for **3ba**, **3d** and **3e**.

At this point, we turned our attention to the intramolecular radical bisheteroarylation process, using **3** as starting material and under our optimized conditions, in the presence of tris(trimethylsilyl)silane and azobisisobutyronitrile (TTMSS/AIBN) under thermal conditions. Previous studies by Motherwell[1d] and Chatgilialoglu[15] suggest that different reaction pathways are

Fig. 2 *cis* and *trans* conformations for the sulfonamides radicals.

Scheme 3 Reaction of pyridine 2-sulfonyl chloride (**6b**) in the presence of 3-bromo-2-aminopyridine (**7b**).
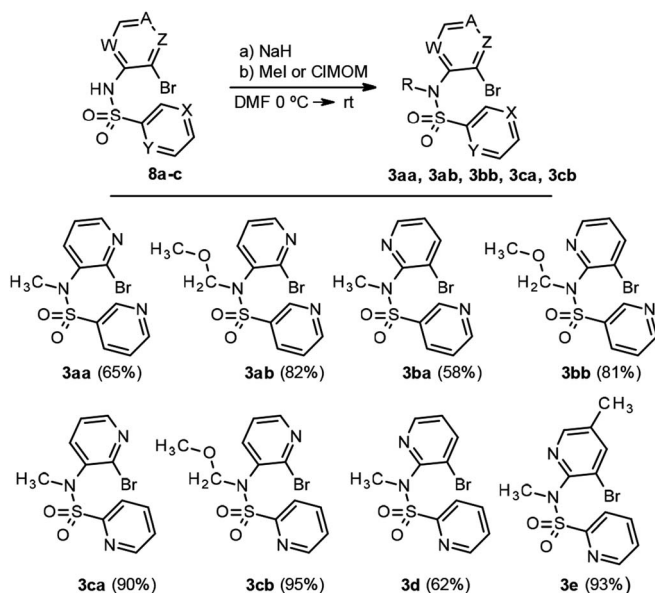
Scheme 4 Proposed *in situ* deprotonation of pyridine sulfonamide **8d** to give the double sulfonylation product **9**.
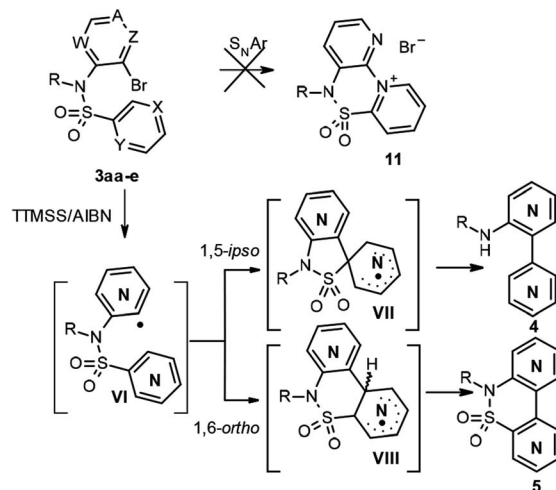

Scheme 5 Methylation of aminopyridines **7b** and **7c**.

possible, depending on the structure of the starting pyridine **3**, with the main ones being shown in Scheme 7. Thus, **3ca** and **3cb** (X = CH, Y = N and Z = N, A, W = CH) can undergo a non-radical
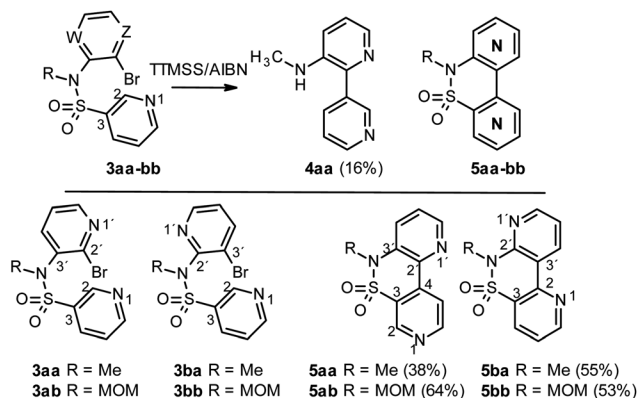

Scheme 6 Results in the preparation of *N*-alkyl sulfonamides **3**.

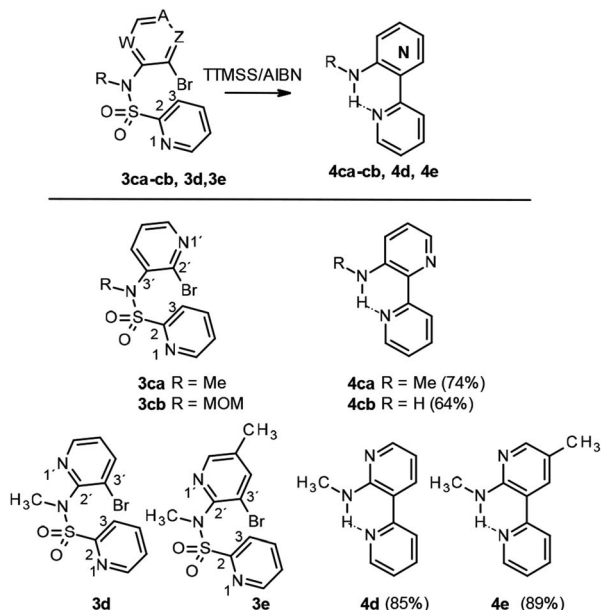**Scheme 7** Some alternative reaction pathways for the bromo sulfonamides **3**.

S$_N$Ar process to give the cyclic derivative **11** due to the nucleophilicity of the pyridine nitrogen and the favourable position of bromide, which can act as a good leaving group, on the other pyridine nitrogen. However, in accordance with previous reports, products **11** were never detected. The other pathways involve the initial formation of heteroaryl radical **VI**, which would evolve by [1,5]-*ipso*-addition to give the spirocyclic radical **VII** and then bipyridines **4**, and/or by [1,6]-*ortho*-addition, in different positions, depending on the starting compound **3**, to give radical **VIII** and, subsequently, **5**.

For the starting material **3** with the sulfonamide group in position C3 (X = N, Y = CH; compounds **3aa-3bb**), in all cases the initial radical **VI** undergoes a [1,6]-*ortho*-attack to yield compounds **5**, whereas the alternative [1,5]-*ipso*-attack was only detected in the case of sulfonamide **3aa**, with product **4aa** being obtained as a by-product of the reaction (<20%; Scheme 8). The experimental evidence points to a trend in the reactivity depending on whether the Br substituent is positioned on either C2' (**3aa** and **3ab**) or C3' (**3ba** and **3bb**) of the attacking pyridine.[16]

Scheme 8 Results in the preparation of compound **5aa-bb**.

Scheme 9 Results in the preparation of compound **4ca-b**, **4d** and **4e**.

Thus, those substrates with a Br in the C2′ position of the pyridine (**3aa** and **3ab**) yield the C4-substituted derivatives as the main products (**5aa** and **5ab**, respectively, Scheme 8) due to the repulsion generated by the proximity of the radical to the non-binding pairs of both nitrogens in the adduct intermediate. In contrast, for those with a Br in position C3′ of the pyridine (**3ba** and **3bb**), the main product results from the attack at C2, which yields products **5ba** and **5bb**, respectively.

Conversely, for compounds **3** with the sulfonamide group placed in position C2 (Y = N, X = CH; compounds **3ca-b**, **3d** and **3e**) and a Br substituent in positions C2′ and C3′ (Scheme 9), the initial radical **VI** undergoes [1,5]-*ipso*-attack to yield the spirocyclic radical **VII** and, subsequently, compounds **4**. For the alternative [1,6]-*ortho*-attack, we were only able to detect traces of compounds **5** (if at all). The experimental data indicate that, irrespective of the position of the pyridine nitrogen in N1′, the

reaction evolves towards the formation of product **4** with an intramolecular hydrogen bond in all cases, with the primary or secondary amine acting as H-donor and the pyridine N1 as H-acceptor.

In order to check other referable cases, we tried to prepare sulfonamides **3** from the commercially available products 4-bromo-3-aminopyridine **7c** and 3-bromo-4-aminopyridine **7d**, but our attempts were unsuccessful. Notably, for compound **3cb**, which contains a MOM group in the starting material, a concomitant deprotection of MOM group was observed during work-up, thus giving easy access to the unsubstituted amine.[17] These results are summarized in Scheme 9.

The identity of these compounds was elucidated by NMR experiments and the structure of one of them (compound **5ba**) unequivocally confirmed by X-ray crystallographic analysis (Fig. 3 and ESI†).

Conclusions

In summary, our results show that intramolecular radical [1,5]-*ipso* and [1,6]-*ortho* substitutions offer a method for the preparation of aminobipyridines or bipyridine sultams when a sulfonamide linker connects the attacking pyridyl radical to the pyridine under attack. For derivatives with a sulfonamide group at the C3-position of the starting pyridine, the [1,6]-*ortho* substitution product was identified in all cases. For substrates with the sulfonamide group at the C2-position, mainly aminobipyridines were obtained, being the leading event the formation of an intramolecular hydrogen bond between the primary or secondary amine as H-donor, and the pyridine N1 as H-acceptor. These sulfonamides with a MOM group in the starting material underwent deprotection of the MOM group during work-up, thus allowing easy access to the unsubstituted amine.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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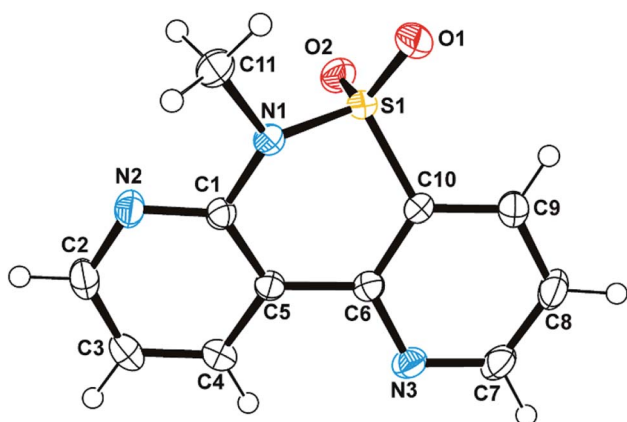

Fig. 3 ORTEP diagram for compound **5ba**. Thermal ellipsoids are drawn at the 50% probability level.

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