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New Intramolecular Cyclization and Rearrangement Processes Based on the Radical Aryl-Aryl Coupling of Arylsubstituted 2-Azetidinones

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Abstract: New polycyclic 2-azetidinones having fused or not biaryl units are easily prepared by the tin-mediated, intramolecular aryl-aryl radical cyclization of readily available arylsubstituted 2-azetidinones. The regioselectivity and efficiency of the process is determined both by the length of the linking chain through the β-lactam nucleus and by the number and position of the substituents on the aromatic acceptor ring.

The strain of the 2-azetidinone ring has been claimed as responsible for the biological activity of β-lactam antibiotics.[1] This fact confers this nucleus with unique properties[2] and makes β-lactams exceptional playgrounds to discover new reactivity. Different fragmentation and/or rearrangement processes have been found while developing new cyclization reactions, or have been observed in specifically designed substrates.[3] Cyclization strategies based on different approaches have been used to build bi- and polycyclic β-lactam systems, radical cyclizations being relative newcomers to this arena.[4] In spite of its synthetic potential, the behaviour of the 2-azetidinone nucleus under radical conditions remains still almost unknown. We report here a preliminary study of the aryl-aryl radical cyclization[5] route to novel polycyclic 2-azetidinones having fused or not biaryl units[6] starting from readily available arylsubstituted 2-azetidinones, as well as the behaviour of radicals adjacent to the 2-azetidinone ring.

Substrates for cyclization, 2-azetidinones **1a-i** were prepared in good yields by the usual ketene-imine cycloaddition (Table). The reaction of acetoxyacetyl chloride and imines derived from *o*-bromoanilines formed *trans*-2-azetidinones **1a-c** as single diastereomers. The remaining *cis*-2-azetidinones **1d-1i** were obtained from acetoxy- or aryloxyacetyl chlorides and the corresponding imines.[7] All 2-azetidinones were obtained and used as single *cis*- or *trans*- isomers. The outcome of the reaction of the radicals generated from compounds **1** strongly depends on the relative position of both, the radical precursor and the radical acceptor in the 2-azetidinone ring. Thus, treatment of 2-azetidinones **1a-c** with Bu_3SnH/AIBN in benzene under reflux formed smoothly the corresponding condensed tetracyclic biaryl-2-azetidinones **2a-c** as single diastereomers (60-70%, isolated yield) together with small amounts of reduced starting material.[8, 9] Reaction of β-lactam **1d** with the radical precursor on C4 and the aromatic acceptor on the lactam nitrogen does not form any cyclized products. In fact, the crude reaction mixtures contained reduced starting 2-azetidinone together with variable amounts of

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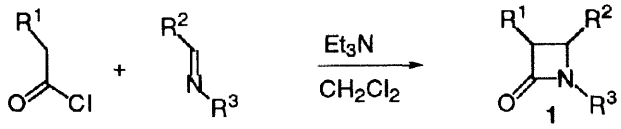
unreacted starting material. However, albeit in low yield, 2-azetidinone **1e**, having other radical acceptor on C3, formed biaryl-2-azetidinone **3a** (15%, isolated yield), with reduced starting 2-azetidinone being the main reaction product (Scheme 1).

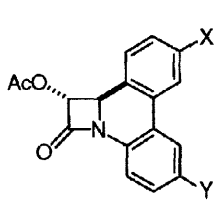
Table. Synthesis of substrates for radical cyclization, **1**.



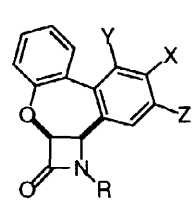
Comp	R^1	R^2	R^3	Yield(%)[a]
trans-**1a**	AcO	PMP[b]	*o*-BrC_6H_4	60
trans-**1b**	AcO	PMP	2-Br,4-MeC_6H_3	72
trans-**1c**	AcO	Ph	*o*-BrC_6H_4	63
cis-**1d**	AcO	*o*-BrC_6H_4	PMP	59
cis-**1e**	PhO	*o*-BrC_6H_4	PMP	75
cis-**1f**	*o*-BrC_6H_4O	PMP	Bn	80
cis-**1g**	*o*-BrC_6H_4O	2,4,6-$(MeO)_3C_6H_2$	Bn	71
cis-**1h**	AcO	2,4,6-$(MeO)_3C_6H_2$	*o*-BrBn	85
cis-**1i**	*o*-BrC_6H_4O	3,5-$(MeO)_2C_6H_3$	Bn	56

[a] Yield of pure, isolated product with correct analytical and spectral data. [b] PMP = 4-$MeOC_6H_4$.

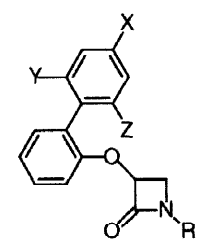
Substrate **1f** with the radical precursor on the C3 group and the aryl acceptor on C4 of the 2-azetidinone nucleus behaved differently. Thus, β-lactam **1f** reacted with Bu_3SnH/AIBN in boiling benzene, to yield the expected cyclization product **3b** (minor product, 20%) together with the new C4-dearylated 2-azetidinone **4a** as the main reaction product (40%), and dehalogenated starting 2-azetidinone (15%). Furthermore, analogous treatment of 2-azetidinone **1g** formed exclusively the rearranged product **4b** (80%, isolated yield), showing that the rearrangement process may be controlled by placing two additional methoxy groups in positions 2 and 6 (*ortho*-disubstitution) on the aryl acceptor moiety. To test this hypothesis 2-azetidinone **1h** was submitted to Bu_3SnH/AIBN treatment. In this case, the cyclization process may be disfavored towards the rearrangement pathway (see below). In fact, C4-unsubstituted 2-azetidinone **5** was exclusively formed (75%, isolated yield). On the other hand, the placement of two methoxy groups in positions 3 and 5 (*meta*-disubstitution), e.g. **1i**, yielded the cyclization product **3c** (60%, isolated yield) as the sole observed product.



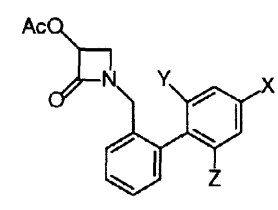
2a: X = OMe, Y = H
2b: X = OMe, Y = Me
2c: X = Y = H



3a: R = PMP, X = Y = Z = H
3b: R = Bn, X = OMe, Y = Z = H
3c: R = Bn, X = H, Y = Z = OMe



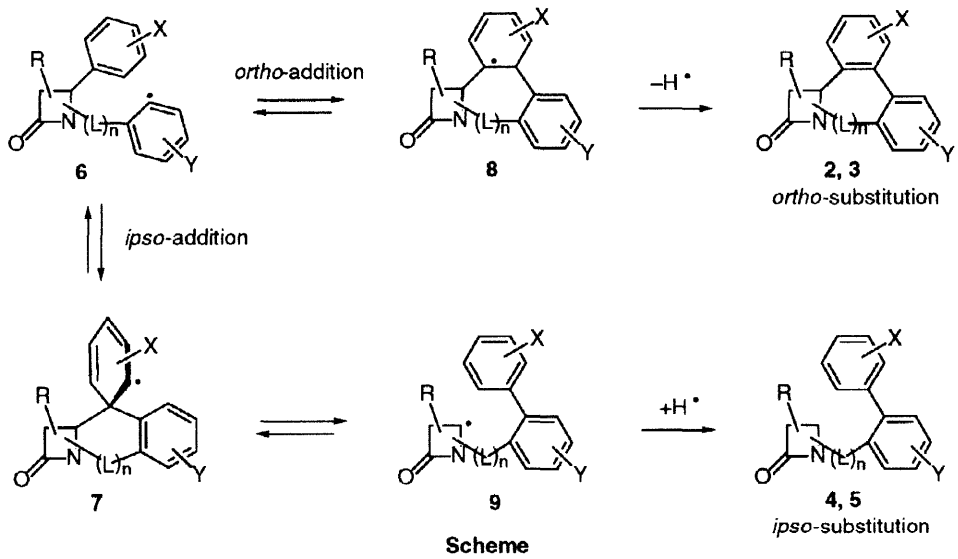
4a: R = Bn, X = OMe, Y = Z = H
4b: R = Bn, X = Y = Z = OMe



5: X = Y = Z = OMe

The results above show that either cyclization or C4-dearylated rearranged products may be regioselectively obtained by choosing the appropriate structure of the precursor. Thus, placing three methoxy groups at the 2, 4, and 6 positions (compounds **1g** and **1h**) led exclusively to *ipso*-substitution reactions (compounds **4a** and **4b**, respectively), whereas the presence of two methoxy groups at the 3 and 5 positions (compound **1i**) resulted in the formation of *ortho*-substitution product (compound **3c**).

The behaviour of the tested substrates may be rationalized through a competition between *ortho*-addition over an *ipso*-addition from the initially formed aryl radical **6** (Scheme). For *N*-(*o*-bromoaryl)-β-lactams (n = 0, substrates **1a-c**), exclusive formation of phenanthridine condensed 2-azetidinones **2a-c** would be accounted through cyclohexadienyl radical **8** resulting from 1,6-addition (*ortho* addition) in the former radical **6**. Had a 1,5-addition been produced, rearrangement products related to **5** would have been observed in these cases. For compounds **1d-i**, with an extra link between the two aromatic rings (n = 1; L = O, CH_2), the competition between the 1,6-addition (*ipso*), and the 1,7-addition (*ortho*) could explain the obtained results. Thus, addition of radical **6** to the neighbouring aromatic ring can operate through an *ipso*-addition to give the spirocyclohexadienyl radical **7** or alternatively *via* an *ortho*-addition to form the isomeric cyclohexadienyl radical **8**. Radical **7**, that benefits from the additional stabilization offered by the oxygen atoms of the methoxy groups placed on appropriate positions (*ortho* or *para*) in the aromatic acceptor ring, promotes the breakage of the C4-C_{ipso} bond. In this way, rearranged compounds of type **4** and **5** are obtained as the major or exclusive products of the reactions. The regeneration of aromaticity and formation of a more stable azetidin-2-on-4-yl radical **9**,[10] could provide the necessary driving force for these reactions. Alternatively, the cyclohexadienyl radical **8** derived from *ortho* attack would evolve to cyclization products **3** but not to rearranged products. The presence of *meta*-methoxy groups in the acceptor ring could lead to direct stabilization of the intermediate radical **8**, and cyclization product **3c** is the only observed product in this case. This result clearly indicates that the location of two *meta* methoxy groups exerts a dominant directing effect which totally eliminates *ipso*-substitution products (type **4**).



Scheme

In summary, preliminary results in the radical cyclization and/or rearrangement of aryl substituted 2-azetidinones have been discussed. Novel polycyclic 2-azetidinones having fused or not biaryl units have been

prepared, and a new rearrangement of the 2-azetidinone nucleus has been uncovered. This rearrangement allows to prepare novel 4-unsubstituted-2-azetidinones, a structural feature present in different compounds of interest such as nocardicines and tabtoxines.[11] The scope and synthetical applications of this new process, as well as the role of the biaryl policyclic products as suicide inhibitors of β-lactamases,[12] and as intermediates in the preparation of different biaryl systems are now being investigated.

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8. To a stirred solution of the corresponding β-lactam **1** (1 mmol), and AIBN (25% w/w) in refluxing dry benzene (215 mL), Bu_3SnH was added. The mixture was refluxed until complete dissapareance of the starting product (t.l.c.). It is notable that slow addition (syringe pump) was no required for these reactions.
9. Compounds **2a-c** are, formally, phenanthridine derived 2-azetidinones. In fact, the reaction of phenanthridine and different ketenes gave condensed biaryl-2-azetidinones related to **2**. These results fell out the scope of this paper and will bc published in due time.
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