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Aryl pyrrolidinones via radical 1,4-aryl migration and 5-*endo-trig* cyclisation of *N*-(2-bromoallyl)arylcarboxamides

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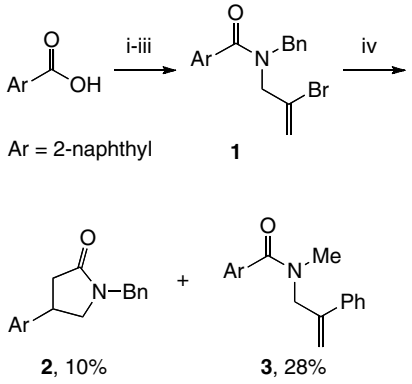
Abstract—Radical reaction of a series of *N*-(2-bromoallyl)arylcarboxamides led to the production of 4-arylpyrrolidin-2-ones and directly reduced materials in comparable yields. A cascade process, involving sequential 5-*exo-trig* spirocyclisation, β-scission, and 5-*endo-trig* cyclisation of the resulting acyl radical, is proposed to explain the pyrrolidinone products.

ipso-Type radical cyclisations onto aromatic rings can result in the formation of spirocycles.[1] For example, since our initial communication on dearomatising radical spirocyclisations onto benzofuran and indole nuclei,[2] radical cyclisations of benzamides, employing samarium iodide[3] and aerobic conditions,[4] and spirocyclisation onto furan derivatives[5] have been reported. In this letter, we present a reaction of vinyl radicals tethered to aromatic rings via an amide that helps to define the scope and limitations of the use of such systems in synthesis.

Naphthalene-2-carboxamide derivative **1** was prepared according to our previously established procedure,[2] although with a disappointingly poor yield for the final alkylation step. When this compound was submitted to standard radical cyclisation conditions,[6] none of the expected spirocycle was isolated; instead, the reaction yielded a substituted pyrrolidinone **2** and a product of phenyl transfer **3** (Scheme 1).



Scheme 1. Reagents and conditions: (i) $(COCl)_2$, DMF, CH_2Cl_2; (ii) $BnNH_2$, NEt_3, CH_2Cl_2, 92% for two steps; (iii) NaH, 2,3-dibromopropene, DMF, 10%; (iv) Bu_3SnH, AIBN, benzene, reflux.

Our mechanistic explanation for the formation of products **2** and **3** is presented in Scheme 2. The initially formed vinylic radical can undergo 5-*exo ipso*-type cyclisation either onto the naphthalene nucleus or onto the phenyl ring of the *N*-benzyl group. The latter-formed spirocycle can then ring-open with rearomatisation[7] to generate a nitrogen-stabilised methylene radical, and then amide **3** following hydrogen atom abstraction. β-Scission of the spirocyclic radical arising from addition to the naphthalene ring would result in rearomatisation with the production of amidoyl radical **4**[8] which can cyclise in an overall 5-*endo-trig* sense[9] to give pyrrolidinone derivative **2**. An alternative 4-*exo*$_{C=C}$/3-*exo*$_{C=O}$/β-scission pathway from **4** → **2** is discounted on the basis of a lack of precedent for radical ring expansion of lactams[10] and because none of the β-lactam **5**, a likely product of radical **6**, was observed.

In order to investigate this process further we decided to synthesise a selection of aromatic amides, this time having a methyl group in place of benzyl, thus removing the possibility of competing phenyl transfer. Also, the strategy for amide formation was modified so as to avoid the low-yielding secondary amide alkylation with 2,3-dibromopropene. Thus, the use of 2-bromoallyl amine,

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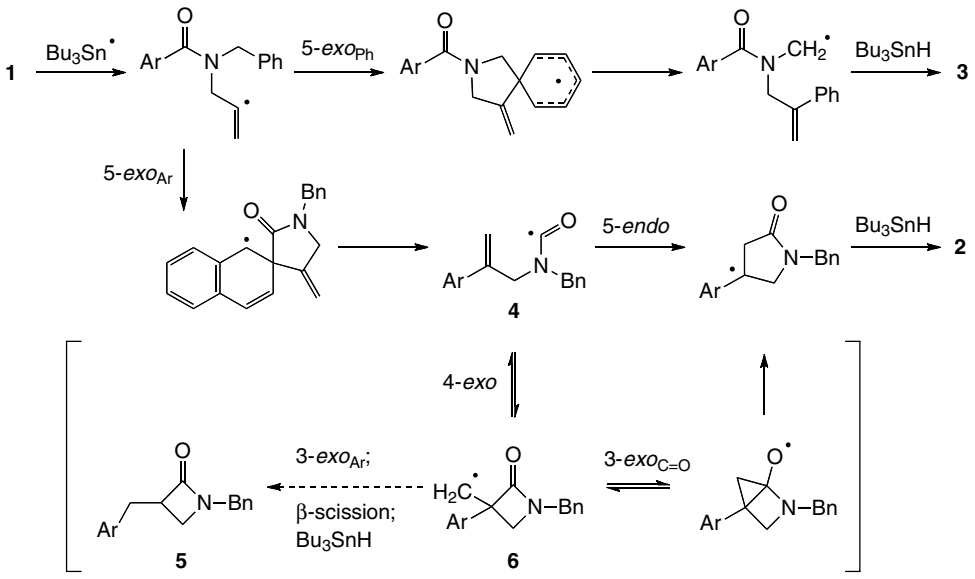


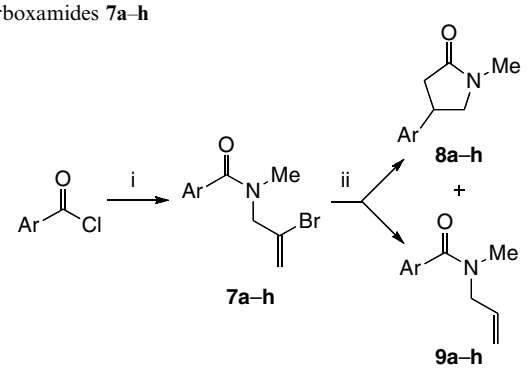
Scheme 2. (Ar = 2-naphthyl).

prepared following Bottini's procedure,[11] in the amide-forming step was followed by N-methylation (→**7**) with good overall yields. The yields for these two steps and the results of the radical reactions are summarised in Table 1.

Formation of the 4-substituted pyrrolidinones **8a**–**h** was observed with examples of *ortho*-, *meta*- and *para*-substituted benzamides; in all cases, these lactams were formed in competition with the directly reduced products **9a**–**h**. Attempts to optimise the reaction conditions (e.g., by varying the rate of Bu_3SnH addition or reaction temperature[12]) did not improve the outcome significantly and the ratio of rearranged (**8**) to reduced (**9**) products was generally approximately 1:1. As an explanation for this insensitivity to the reaction conditions, we envisaged possible formation of the reduced products by 1,4-hydrogen abstraction[13] from the amide methyl followed by reduction of the *N*-methylene radical. However, in the radical reaction of amide **7a** with Bu_3SnD, the ^2H NMR spectrum of the reduced product indicated deuterium incorporation only at the olefinic methine which effectively eliminated this explanation. On this basis, we conclude that the product profile is dictated largely by the relative population of *s-cis* and *s-trans* amide rotameric radicals (Fig. 1) that interconvert slowly relative to their lifetimes under the reaction conditions.[14]

The observation that the highest yield of the rearrangement product **8** was obtained in the reaction of 4-(trifluoromethyl)benzamide derivative **7d** may indicate a favourable polarity effect on the rate of the first 5-*exo* cyclisation, however, no clear trend arises from the reactions of analogous substrates **7a**–**c** to support this. Finally, it is noteworthy that the radical reaction of 2-pyrrolecarboxamide **7h** produced the pyrrolidinone **8h** in spite of an expectation that a spirocyclic product

Table 1. Isolated yields for the synthesis and radical reactions of aryl carboxamides **7a**–**h**



Reagents and conditions: (i) 2-bromoallylamine, aq. NaOH. CH_2Cl_2; then NaH, MeI, DMF; (ii) Bu_3SnH, AIBN, benzene, reflux.

Entry	Ar	**7** (%)	**8** (%)	**9** (%)
a	*p*-Anisyl	71	37	41
b	*p*-Tolyl	77	35	38
c	Phenyl	63	30	35
d	*p*-(Trifluoromethyl)phenyl	69	46	27
e	*o*-Tolyl	66	28	Not isolated
f	*m*-Tolyl	64	36	34
g	*m*-Anisyl	52	38	35
h	*N*-Methyl-2-pyrrolyl	69	33	30

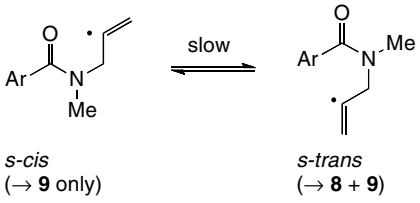


Figure 1.

would result based on the similar cases described by Jones et al.[15]

In summary, we have demonstrated the operation of sequential radical 1,4-aryl migration and formal 5-*endo-trig* cyclisation of 1-(arylcarboxamido)prop-2-en-2-yl radicals in which the amide nitrogen bears an alkyl group. In a future report, we will describe our study of the synthesis and radical reactions of substrates designed to address the limitations caused by rotameric preferences about the amide group.

Acknowledgements

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