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Radical cascade involving a 5-*endo*-*trig* cyclization of α-amidoyl radicals

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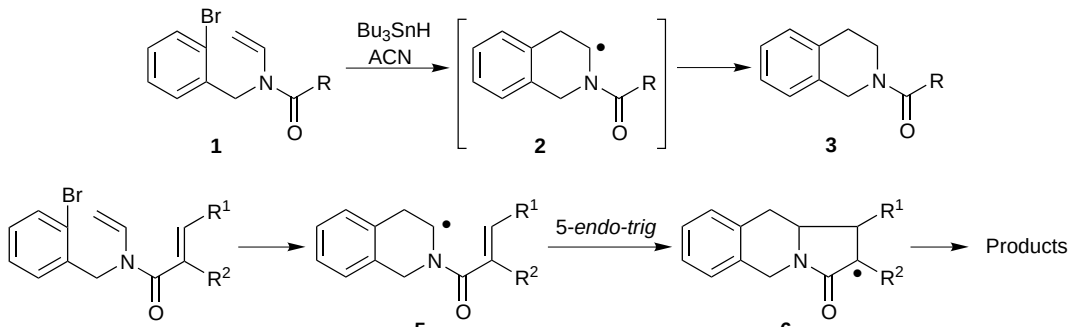
Abstract—Bu_3SnH-mediated radical reactions of aryl bromides **4** gave pyrrolo[1,2-*b*]- and isoindolo[2,1-*b*]isoquinoline derivatives **11** through a radical cascade process involving a 6-*endo*-*trig* cyclization of an aryl radical and a 5-*endo*-*trig* cyclization of an α-amidoyl radical.

Radical cascade approaches to polycyclic compounds are now widely used in organic and natural products syntheses.[1] To evaluate the synthetic utility of new radical reactions, these methods have frequently been applied to radical cascade processes. We recently reported the first example of a 6-*endo* selective aryl radical cyclization onto a simple alkenic bond. Enamides **1**, on treatment with Bu_3SnH in the presence of ACN (azobiscyclohexanecarbonitrile) in boiling toluene, underwent 6-*endo*-*trig* aryl radical cyclization to give tetrahydroisoquinolines **3** via intermediate α-amidoyl radicals **2** (Scheme 1).[2] In the present study, we examined the radical cascades of a range of *N*-acryloyl congeners **4** to determine the feasibility of using a 5-*endo*-*trig* radical cyclization of α-amidoyl radicals **5**. In this paper, we describe the viability of this sequence for the synthesis of pyrrolo[1,2-*b*]- and isoindolo[2,1-*b*]isoquinolines.[3]

We initiated our investigation by examining the cyclization of enamide **4a**, which was prepared from amine **7**[2] according to the procedure illustrated in Scheme 2. A toluene solution of **4a** was treated at reflux with a solution of 1.5 equiv. of Bu_3SnH and a catalytic



4a: $R^1 = R^2 = H$
4b: $R^1 = Me$, $R^2 = H$
4c: $R^1 = H$, $R^2 = Me$
4d: $R^1 = R^2 = Me$
4e: $R^1, R^2 = -(CH_2)_4-$

Scheme 1.

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amount of ACN in toluene over a period of 3.5 h to give a complex mixture of products, from which three products, **8a**, **9a**,[4] and **10a**,[4] were isolated in 11, 13 and 3% yields, respectively (Scheme 3). Unfortunately, enamide **4a** gave no expected radical cascade product. Formation of **9a** and **10a** might be a result of 6-*exo* and 7-*endo* aryl radical cyclizations with the *N*-acryloyl group, respectively. The *N*-crotonoyl congener **4b** also gave no radical cascade product and afforded only the 6-*endo* and 6-*exo* aryl radical cyclization products **8b** and **9b** in 39 and 28% yields, respectively. In this instance, no 7-*endo* cyclization product **10b** was formed (Scheme 3).

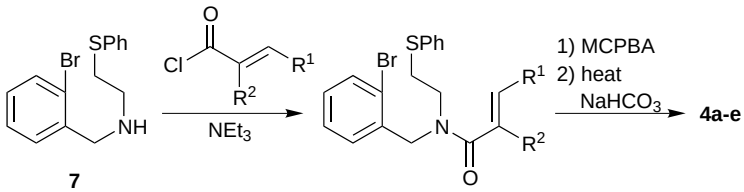
The reason for the low overall yield of **8a** and **9a** is obscure at the moment, since the starting enamide **4a** and the products **8a** and **9a** were relatively stable in boiling toluene and only a limited quantity of the simple reduction product was formed.

We soon found, however, that treatment of the *N*-methacryloyl congener **4c** with Bu_3SnH/ACN gave the expected radical cascade product, 1,2,3,5,10,10a-hexahydro-2-methylpyrrolo[1,2-*b*]isoquinolin-3-one (**11c**),[4] in 26% yield as a mixture of two stereoisomers in a ratio of ca. 3:2, together with **8c** and **10c** in 25 and 8% yields, respectively (Scheme 4).

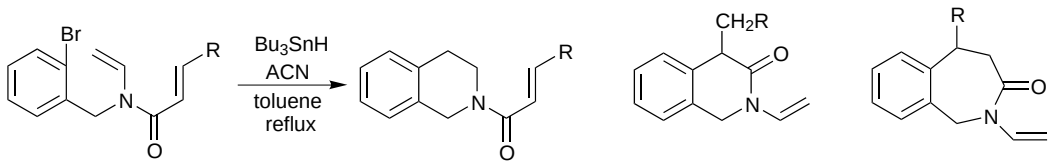
Formation of **11c** strongly suggests that the methyl substituent at the α-position of the *N*-acryloyl group of **4c** acts as an effective radical-stabilizing group for the radical **6** (Scheme 1: $R^1=H$, $R^2=Me$) generated by 5-*endo*-*trig* cyclization of α-amidoyl radical **5**. The methyl group might also prevent the formation of the 6-*exo* cyclization product such as **9** due to steric reasons.

Encouraged by the success in obtaining the radical cascade product **11c** from **4c**, we next turned our attention to the tiglyl derivative **4d**. Treatment of **4d** with Bu_3SnH/ACN in boiling toluene gave **8d**, **10d** and **11d** in 18, 3 and 57% yields, respectively (Scheme 4). The ^1H NMR spectrum of **11d** indicated it to be a mixture of two stereoisomers in a ratio of ca. 3:2. The *N*-crotonoyl derivative **4b**, having a β-methyl substituent on the acryloyl group, gave no 5-*endo*-*trig* cyclization product, indicating that the β-methyl substituent does not play a part in effecting the 5-*endo*-*trig* cyclization of α-amidoyl radicals. In this context, it is of interest that the yield of **11d** (57%) was much higher than that of **11c** (26%). Similarly, enamide **4e** afforded isoindolo[2,1-*b*]isoquinoline derivative **11e**[4] in 36% yield as a single stereoisomer, along with **8e** and *trans*-**10e** in 31 and 4% yields, respectively (Scheme 5).[5] The stereochemistry of **11e**, as depicted in Scheme 5, was confirmed by NOE experiments.

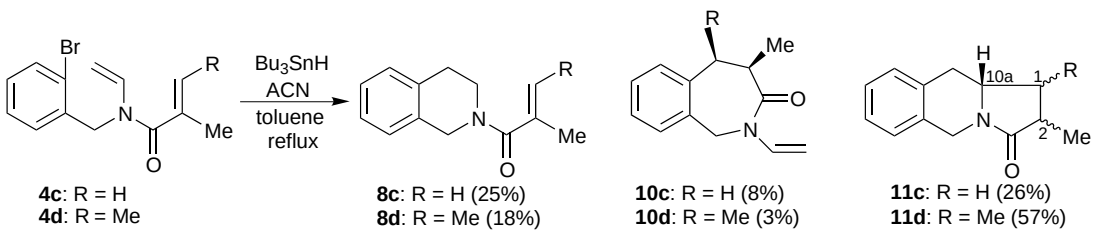
5-*endo*-*trig* Ring-closure has been recognized as a stereoelectronically disfavored process not only for heterolytic reactions, but also for homolytic cyclizations.[6]



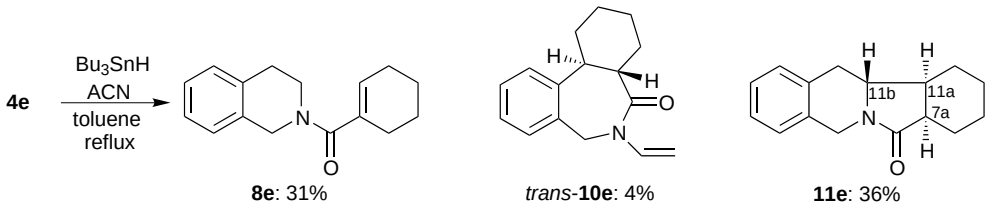
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

However, not unnaturally, several exceptions to this guideline have been discovered.[7,8] Quite recently, the first example of 5-*endo*-*trig* cyclization of an α-amidoyl radical has also been reported.[9,10] Although many examples are required to determine the factors involved in effecting the 5-*endo*-*trig* cyclization of α-amidoyl radicals, the present method may be useful for the synthesis of poly-heterocyclic compounds.

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4. Spectroscopic data for products (diagnostic data only). **9a**: IR ($CHCl_3$) 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.53 (d, 3H, $J=7.3$ Hz, Me), 3.65 (q, 1H, $J=7.3$ Hz, 4-H), 4.55 (dd, 1H, $J=9.2$, 1.3 Hz), 4.64 (dd, 1H, $J=16.2$, 1.3 Hz), 7.58 (dd, 1H, $J=16.2$, 9.2 Hz). **10a**: IR ($CHCl_3$) 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 3.05 (br t, 2H, $J=$ca. 7 Hz), 3.25 (br t, 2H, $J=$ca. 7 Hz), 4.46 (dd, 1H, $J=9.2$, 1.3 Hz), 4.63 (dd, 1H, $J=16.2$, 1.3 Hz), 7.37 (dd, 1H, $J=16.2$, 9.2 Hz). **11c**: IR ($CHCl_3$) 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.27 (d, 3H, $J=6.9$ Hz, Me for both isomers A and B), 1.35–1.46 (m, 3/5H, one of 1-H for isomer A), 1.94–2.15 (m, 2/5×3H, 1-H and 2-H for isomer B), 2.52–2.70 (m, 3/5×3H, one of 1-H, 2-H and one of 10-H for isomer A), 3.61–3.74 (m, 3/5H, 10a-H for isomer A), 3.72–3.84 (m, 2/5H, 10a-H for isomer B). **11e**: IR ($CHCl_3$) 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.18 (dq, 1H, $J=4.3$, 6.9 Hz, 11a-H), 2.53 (q, 1H, $J=6.9$ Hz, 7a-H), 3.46 (dt, 1H, $J=11.6$, 4.3 Hz, 11b-H).
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