

6-Endo-trig and 5-exo-trig selective aryl radical cyclisations of *N*-(*o*-bromobenzyl) enamides

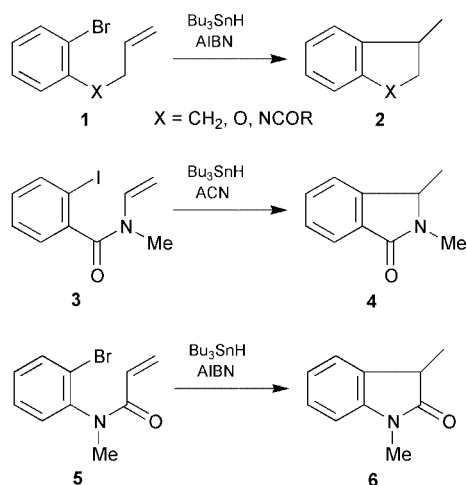
Hiroyuki Ishibashi,* Issei Kato, Yoshifumi Takeda, Momoyo Kogure and Osamu Tamura

Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920-0934, Japan.
E-mail: isibashi@db.s.p.kanazawa-u.ac.jp

Received (in Cambridge, UK) 11th May 2000, Accepted 28th June 2000

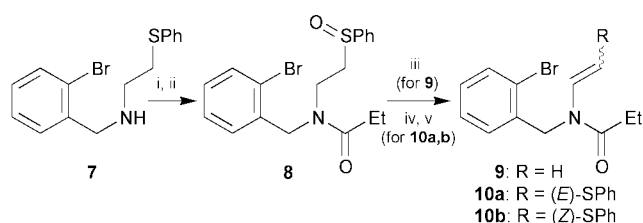
Bu₃SnH-mediated aryl radical cyclisation of enamide **9 proceeded in a 6-endo-trig manner to give exclusively tetrahydroisoquinoline derivative **12**, whereas enamide **10b** having a (*Z*)-phenylthio group at the terminus of the *N*-vinyl bond gave exclusively the 5-exo-trig cyclisation product **16**.**

Aryl radical cyclisations are now widely used in organic synthesis for the construction of fused aromatic compounds. A 5-exo-trig cyclisation is generally preferred over a 6-endo-trig ring closure in those systems having an alkenic bond at the 5-position relative to the aryl radical centre. For example, aryl bromides **1** (X = CH₂, O or NCOR), upon treatment with Bu₃SnH in the presence of AIBN, gave almost exclusively the 5-exo cyclisation products **2**.¹ This was also the case for the



cyclisations of enamide **3** and acryloylanilide **5**, which gave only the five-membered lactams **4**² and **6**.^{3,4} respectively. Herein we wish to report that *N*-(*o*-bromobenzyl) enamide **9** undergoes aryl radical cyclisation in a 6-endo-trig manner to give exclusively tetrahydroisoquinoline derivative **12**, and that the mode of cyclisation can be shifted to a 5-exo-trig manner by introducing a (*Z*)-phenylthio group at the terminus of the *N*-vinyl bond.

The requisite radical precursors **9**, **10a** and **10b** were prepared as shown in Scheme 1.

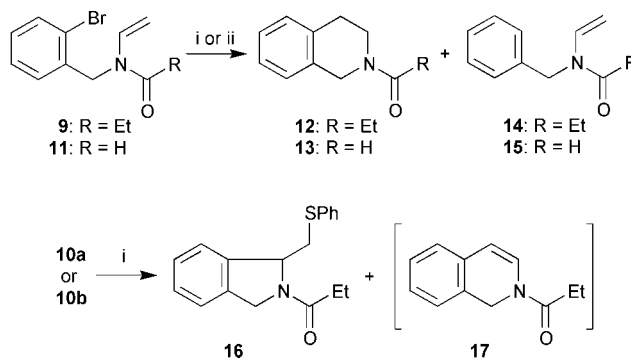


Scheme 1 Reagents and conditions: i, EtCOCl, Et₃N, CH₂Cl₂, rt, 90%; ii, MCPBA, CH₂Cl₂, 0 °C, 93%; iii, xylene, NaHCO₃, reflux, 81%; iv, (CF₃CO)₂O, CH₂Cl₂, rt; v, toluene, reflux, 46% for **10a**, 13% for **10b** (based on **8**).

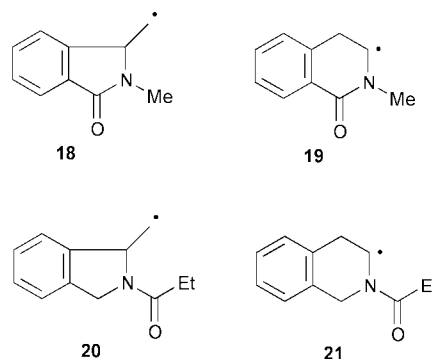
When a mixture of Bu₃SnH (2.2 eq.) and azobis(cyclohexanecarbonitrile) (ACN) (0.4 eq.) in toluene was added slowly to a boiling solution of **9** in toluene over a period of 3.5 h, the 6-endo cyclisation product **12**⁵ was obtained in 68% yield, along with the simple reduction product **14** (16% yield) (Scheme 2). Similarly, the *N*-formyl congener **11** gave **13** and **15** in 43 and 19% yields, respectively. On the other hand, treatment of the sulfur substituted (*E*)-isomer **10a** with Bu₃SnH–ACN afforded the 5-exo cyclisation product **16** in 40% yield, along with dihydroisoquinoline derivative **17** in 41% yield. The corresponding (*Z*)-isomer **10b** gave **16** as a sole product in 75% yield.

The exclusive formation of the 6-endo cyclisation product **12** from **9** is of great interest in view of previous work on radical cyclisations of the related compounds **1**, **3** and **5**, which gave the 5-exo cyclisation products **2**, **4** and **6**, respectively. Formation of **4** (from **3**) and **12** (from **9**) can be rationalized by an attack of Bu₃SnH on the primary radical **18** and on the secondary radical **21**, respectively. Since enamide **3** gave no 6-endo cyclisation product via the secondary radical **19**, formation of **12** from **9** could not be explained by assuming that the nitrogen-substituted secondary radical **21** might be more stable than the primary radical **20**.

One possible explanation for the formation of **12** from **9** may involve a consecutive 5-exo cyclisation and neophyl-like† rearrangement of the resulting radical **20**. The possibility,



Scheme 2 Reagents and conditions: i, Bu₃SnH, ACN, toluene, reflux; ii, Bu₃SnH, Et₃B, toluene, rt.



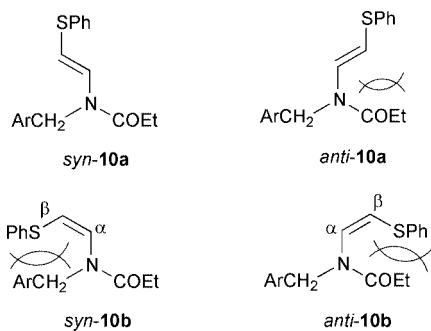


Fig. 1 Ar = *o*-BrC₆H₄.

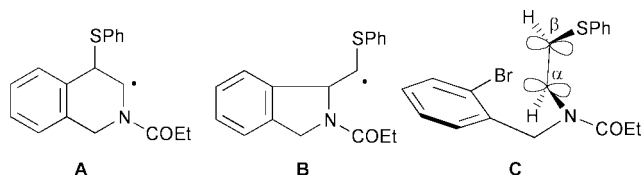
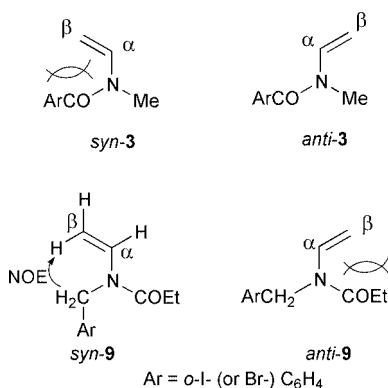


Fig. 2

however, could be ruled out by the following work to simultaneously examine the effects of various Bu₃SnH concentrations, addition times and reaction temperatures.⁶ Thus, treatment of **9** with 4 eq. of Bu₃SnH (not using the slow addition technique) in the presence of triethylborane in toluene at rt for 16 h also gave the 6-*endo* cyclisation product **12** in 51% yield, along with the reduction product **14** (23%). The most plausible explanation for the results with **3** and **9**, therefore, may be derived from the consideration of the rotation of enamide.⁷ Two conformers can be considered for both radical precursors, *i.e.* *syn*-**3** and *anti*-**3** for **3** and *syn*-**9** and *anti*-**9** for **9**. In the



Ar = *o*-I- (or Br-) C₆H₄

conformers *syn*-**3** and *anti*-**9**, severe steric repulsions between the aryl (*o*-IC₆H₄CO) and C=C groups and between the acyl (EtCO) and C=C groups, respectively, are evident. The conformers *anti*-**3** and *syn*-**9** therefore predominate, and the resulting radicals attack the more proximate C_α-position of *anti*-**3** and C_β-position of *syn*-**9**, to give the observed 5-*exo* cyclisation product **4** and the 6-*endo* cyclisation product **12**, respectively. The NOE difference spectroscopy also indicated that **9** exists only in the *syn*-**9** form.⁸ Thus, irradiation of the signals due to the *N*-benzylic protons [δ 4.76 ($\frac{1}{2} \times 2$ H, s) and 4.94 ($\frac{3}{2} \times 2$ H, s)] of **9** caused an enhancement of the signals due to the C_β-proton *cis* to the nitrogen atom [δ 4.26 ($\frac{1}{2}$ H, d, *J* 15.6) and 4.29 ($\frac{3}{2}$ H, d, *J* 15.6)] and no enhancement of the signals due to the C_α-proton [δ 6.95 ($\frac{3}{2}$ H, dd, *J* 15.6 and 9.2) and 7.67 ($\frac{1}{2}$ H, dd, *J* 15.6 and 9.2)].¹¹ The preponderance of the *syn*-**9** conformer over *anti*-**9** seems to be independent of the size of the *N*-acyl group, since **11** having a sterically less demanding *N*-formyl group, also gave the 6-*endo* cyclisation product **13**.

For the sulfur substituted (*E*)-isomer **10a**, the two conformers *syn*-**10a** and *anti*-**10a** can be considered (Fig. 1). As in the case of *anti*-**9**, there is a severe steric repulsion between the EtCO and C=C groups in *anti*-**10a**, and the cyclisation might therefore proceed *via* the conformer *syn*-**10a** in a 6-*endo* manner to give **17** through an elimination of a benzenethiyl radical from the resulting intermediate radical **A** (Fig. 2). The major product of the reaction of **10a**, however, is the 5-*exo* cyclisation product **16**. This is probably because the sulfur atom of the intermediate radical **B** can strongly stabilise the neighboring radical centre.⁹

On the other hand, both conformers *syn*-**10b** and *anti*-**10b** for the (*Z*)-isomer **10b** have a more severe steric constraint between the *o*-BrC₆H₄CH₂ and SPh groups for the former and between the COEt and SPh groups for the latter (Fig. 1), and hence the C_α=C_β bond and amide nitrogen might not be conjugated in enamide **10b**.¹⁰ If the C_α=C_β bond is almost perpendicular to the amide bond, as depicted in **C** (Fig. 2), the resulting radical can attack the more proximate C_α-position to give exclusively the observed 5-*exo* cyclisation product **16**.¹¹

Notes and references

† The IUPAC name for neophyl is 2-methyl-2-phenylpropane.

- For X = CH₂, see: A. N. Abeywickrema, A. L. J. Beckwith and S. Gerba, *J. Org. Chem.*, 1987, **52**, 4072; For X = O, see: S.-K. Chung and F.-F. Chung, *Tetrahedron Lett.*, 1979, 2473; H. Togo and O. Kikuchi, *Tetrahedron Lett.*, 1988, **29**, 4133; For X = NCOR, see: J. P. Dittami and H. Ramanathan, *Tetrahedron Lett.*, 1988, **29**, 45; Y. Özlü, D. E. Cladingboel and P. J. Parsons, *Tetrahedron*, 1994, **50**, 2183.
- H. Ishibashi, K. Ohata, M. Niihara, T. Sato and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 2000, 547.
- K. Jones, M. Thompson and C. Wright, *J. Chem. Soc., Chem. Commun.*, 1986, 115; K. Jones and J. M. D. Storey, *Tetrahedron Lett.*, 1993, **34**, 7797.
- A limited example of 6-*endo* selective cyclisation has been reported for the palladium-mediated reaction of *N*-acryloyl-7-bromindoline. See: J. W. Dankwardt and L. A. Flippin, *J. Org. Chem.*, 1995, **60**, 2312.
- C. Aubert, C. Huard-Perrio and M.-C. Lasne, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2837.
- Careful examinations on the effects of varying Bu₃SnH concentration, addition time and reaction temperature, have frequently shown that 6-*endo* cyclisation products are formed by an initial 5-*exo* cyclisation followed by neophyl rearrangement. See: K. A. Parker, D. M. Spero and K. C. Inman, *Tetrahedron Lett.*, 1986, **27**, 2833; A. N. Abeywickrema, A. L. J. Beckwith and S. Gerba, *J. Org. Chem.*, 1987, **52**, 4072; K. Jones, S. A. Brunton and R. Gosain, *Tetrahedron Lett.*, 1999, **40**, 8935. See also ref. 2.
- An initial conformation of a radical precursor has been suggested to play an important role in deciding the course of cyclisation. See: D. P. Curran and J. Tamine, *J. Org. Chem.*, 1991, **56**, 2746; O. M. Musa, J. H. Horner and M. Newcomb, *J. Org. Chem.*, 1999, **64**, 1022; D. P. Curran, W. Liu and C. H.-T. Chen, *J. Am. Chem. Soc.*, 1999, **121**, 11 012, and references cited therein.
- It has been also suggested that the vinyl groups of *N*-alkyl-*N*-vinylcarbamates occupy *anti*-position to the alkoxycarbonyl groups. See: O. Tamura, M. Hashimoto, Y. Kobayashi, T. Katoh, K. Nakatani, M. Kamada, I. Hayakawa, T. Akiba and S. Terashima, *Tetrahedron*, 1994, **50**, 3889; T. Akiba, O. Tamura, M. Hashimoto, Y. Kobayashi, T. Katoh, K. Nakatani, M. Kamada, I. Hayakawa and S. Terashima, *Tetrahedron*, 1994, **50**, 3905.
- For sulfur-controlled *exo* selective radical cyclisations, see: H. Ishibashi, T. Kobayashi and D. Takamasu, *Synlett*, 1999, 1286 and references cited therein.
- This assumption was supported by IR spectral properties showing the carbonyl band for (*E*)-isomer **10a** in a higher frequency region (1680 cm⁻¹) compared to that (1660 cm⁻¹) for (*Z*)-isomer **10b**.
- It seems that the size of the substituent on the nitrogen atom of **10a,b** does not influence the conformer population. Thus, treatment of the *N*-COBu^t congener of (*E*)-isomer **10a** also gave nearly equal amounts of 5-*exo* cyclisation product (42%) and 6-*endo* cyclisation product (37%), and the corresponding (*Z*)-isomer gave only the 5-*exo* cyclisation product in 70% yield (compare to the results with **10a,b**).