Tandem Radical Translocation and Homolytic Aromatic Substitution: a Convenient and Efficient Route to Oxindoles

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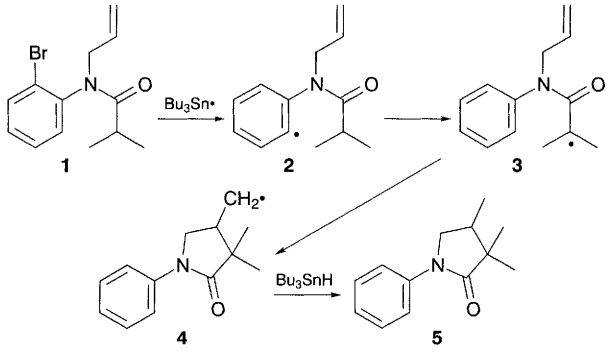
Suitable *o*-bromo-*N*-methylanilides are efficiently converted into oxindoles by treatment with tributylstannane at 160 °C *via* tanden translocation of the initially formed aryl radical and intramolecular homolytic substitution.

Although the propensity of aryl radicals to undertake intramolecular hydrogen-atom transfer from suitably disposed aliphatic side chains was first recognised more than 20 years ago[1,2] the mechanistic features and synthetic utility of this reaction have only recently received serious attention.[3–12] Like alkoxyl radicals,[13] aryl radicals react preferentially through a six-membered transition structure, but examples of 1,4-,[14,15] 1,6-[4,6,9,11,16] and 1,7-[4,6,11,16] transfers have also been recorded. The synthetic exploitation of the reaction involves initial radical translocation to form an alkyl radical which then undergoes further transformations including homolytic substitution,[9] fragmentation,[7,16] rearrangement[5,8] or cyclisation onto a suitably disposed alkenyl substituent.[3,10,12,17]

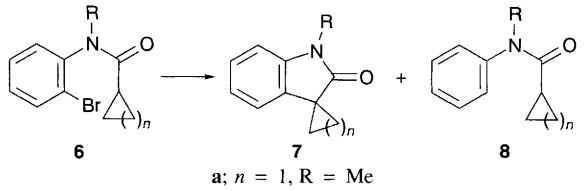
A typical example of tandem radical translocation and cyclisation is provided by the formation of the substituted lactam **5** upon treatment of **1** with tributylstannane (Scheme 1).[17] While determining the kinetics of the individual steps in this and related reactions we found that if a suitable site of unsaturation in the side chain is not available for intramolecular addition the substituted alkyl radical sometimes undergoes homolytic substitution onto the aryl nucleus. We have now defined conditions under which this substitution can be brought about in high yield thus efficiently affording fused-ring systems. The procedure provides a short and convenient method for the preparation of *N*-substituted spiro-oxindoles and related compounds.

Initial exploratory experiments were conducted with the *N*-methyl amide **6a** which was treated with tributylstannane under standard cyclisation conditions, *viz.* 0.1 mol l^{-1} Bu_3SnH in benzene at 80 °C with AIBN initiator. Only two products† were detected by GC: the cyclised spiro-oxidole **7a** (43%) and the directly reduced compounds **8a** (57%). In order to identify which of the radical steps (*i.e.* 1,5 hydrogen atom transfer or cyclisation) is relatively slow and hence favours formation of the reduction product **8a**, the reaction was repeated with tributyltin deuteride. ^2H NMR spectroscopy of the products showed that all of the isotope in **8a** resided in the side chain at C-1 in the cyclopropane ring. This result indicates that the radical translocation step is much faster than the deuterium atom transfer from Bu_3SnD to the aryl radical under the conditions used. Preliminary results of experiments with neat tributyltin deuteride indicate $k > 10^8$ s^{-1} for the 1,5 intramolecular hydrogen atom transfer.[18]

Further mechanistically significant results were obtained from experiments with the bromoacetamide **12** obtained in 80% yield by treatment of **11a** with lithium diisopropylamide and carbon tetrabromide. Heating of **12** with Bu_3SnH under the standard conditions at 80 °C gave mainly the directly reduced compound **11a** with only a very small yield (2%) of the cyclised product **10a** (see Table 1). However, when a mixture of **12** and 0.1 mol l^{-1} Bu_3SnH in *tert*-butylbenzene was heated at 160 °C while a catalytic amount of di-*tert*-butyl peroxide was added every hour over 4 hours the cyclised product **10a** was obtained in good yield (88%). A similar outcome was observed when the aryl bromide **9a** was similarly treated with Bu_3SnH at 160 °C. These results provide further evidence that intramolecular homolytic substitution is the slow step in the sequence leading from aryl bromides such as **6a** or **9a** to the cyclised products



Scheme 1

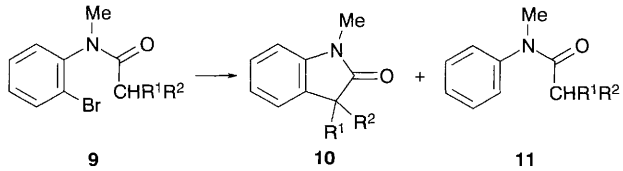


a; n = 1, R = Me
b; n = 2, R = Me
c; n = 3, R = Me
d; n = 4, R = Me
e; n = 4, R = CH_2Ph

Table 1 Yields of oxindoles formed by radical reactions of bromoanilides

		Products and yields (%)				
Method[a]	Reactant	Cyclised	GC	Isolated	Uncyclised	GC
A	**6a**	**7a**	43	40	**8a**	57
C	**6a**	**7a**	99	81	**8a**	1
B	**6b**	**7b**	75	62	**8b**	25
B	**6c**	**7c**	79	nd[b]	**8c**	21
C	**6c**	**7c**	96	87	**8c**	13
A	**6d**	**7d**	20	nd[b]	**8d**	80
B	**6d**	**7d**	79	nd[b]	**8d**	21
C	**6d**	**7d**	100	85	**8d**	—
C	**6e**	**7e**	87	80	**8e**	13
B	**9a**	**10a**	90	70	**11a**	10
C	**9c**	**10c**	56	47	**11c**	44
C	**9b**	**10b**	62	51	**11b**	38
A	**12**	**10a**	2	nd[b]	**11a**	98
B	**12**	**10a**	88	66	**11a**	12

[a] A: 0.1 mol l^{-1} Bu_3SnH in benzene at 80 °C; B: 0.1 mol l^{-1} Bu_3SnH in *tert*-butylbenzene at 160 °C with addition of di-*tert*-butyl peroxide in small portions; C: Syringe pump addition of Bu_3SnH and di-*tert*-butyl peroxide to the substrate in *tert*-butylbezene at 160 °C. [b] Yield not determined.



a; R^1 = R^2 = Me
b; R^1 = Me; R^2 = H
c; R^1 = R^2 = H

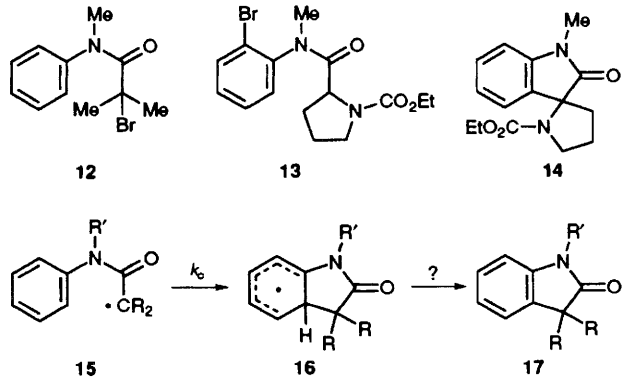
while the dramatic change in the course of the reaction with increase in temperature indicates that at least one of the steps involved in the substitution has a relatively high energy of activation.

The results of cyclisations affording a variety of substituted spiro oxindoles are summarised in Table 1. Of the reactions conducted at 80 °C only the cyclisation of **6a** affords synthetically useful amounts of cyclic products. The greater efficiency of this cyclisation by comparison with those of **6d** and **12** probably reflects the difference in reactivity of the intermediate tertiary radicals. The substituted cyclopropyl radical derived from **6a** is expected to be similar to a vinyl radical in its reactivity[19] and as such is more reactive than the radicals derived from **6d** and **12**.

When the reaction was conducted at 160 °C all the substrates studied gave good to excellent yields of cyclised products as measured by GC. The isolation of products was sometimes difficult. The best procedure involved treatment of the crude mixture with aqueous sodium fluoride followed by chromatography. The outcome of the cyclisation of **9c** is especially significant because of the difficulty of obtaining oxindoles alkylated solely on nitrogen by alternative methods; *e.g.* alkylation of oxindole often proceeds with poor regioselectivity. The successful cyclisation of **13** to give **14** (87%) is also of especial interest because it provides a model for the synthesis of the spirocyclic oxindole alkaloid horsfiline.[20] The precursor **13** was readily prepared from the acid chloride of *N*-ethoxycarbonyl proline;[21] ethoxycarbonyl protection was used to reduce the stabilising effect of the nitrogen atom on the intermediate radical.

As identical conditions were employed for most of the reactions conducted at 160 °C, the ratios of cyclised to reduced products for the various substrates should give a measure of the relative values of k_c/k_H, where k_c is the rate constant for the rate determining step of cyclisation and k_H is the rate constant for hydrogen atom transfer from the stannane to the uncyclised radical. The results indicate that this ratio varies little over the range of radicals studied. Even the cyclisation of **13** which involves the intermediacy of a captodatively stabilised radical proceeds in high yield. As expected reducing the effective concentration of tributylstannane by slow (syringe pump) addition of a mixture of tributylstannane and di-*tert*-butyl peroxide to the bromo compound in *tert*-butylbenzene at 160 °C improved the yield of cyclised products.

Although these reactions clearly involve the intermediacy of radicals of the general type **15** the mechanism of formation of the cyclised products has yet to be clarified. Possible steps in the conversion of the cyclohexadienyl radical **16** into the fully aromatic product **17** in the presence of tributylstannane might



involve: (*a*) disproportionation of **16** followed by oxidation of cyclohexadiene derivatives during work-up; (*b*) the oxidation of **16** by AIBN or other initiators as suggested by Curran;[12] or (*c*) a 'pseudo $S_{RN}1$' mechanism in which the key step is the reaction of **16** with tributylstannane in an acid–base process to afford the radical anion of **17**, the tributyltin cation and hydrogen, as proposed by Bowman.[22] Our failure to observe any deuterium in the cyclised product when tributyltin deuteride is used appears to preclude mechanism (*a*), while we doubt the ability of di-*tert*-butyl peroxide to oxidise **16** in the presence of tributylstannane. Hence on the basis of the present available evidence we favour the $S_{RN}1$ type of mechanism.

In summary the experimental conditions described above provide a convenient and efficient method for the preparation of oxindoles from *o*-bromoanilides. It seems likely that similar conditions will allow the preparation of a variety of polycylic systems by tandem radical translocation and aromatic substitution.

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Footnote

† All new compounds gave satisfactory ^{1}H and ^{13}C NMR spectra, and microanalytical data.

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