

COMPETING RADICAL TRANSLOCATION REACTIONS OF TERTIARY N-(2-BROMOBENZYL)- AND N-(8-BROMONAPHTHYL)-ACETAMIDES

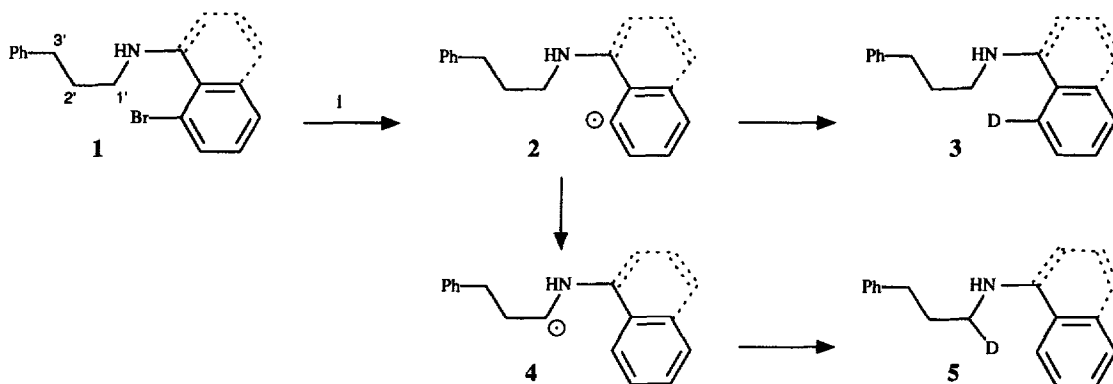
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Abstract: The radical translocation reactions in N,N-disubstituted acetamides **10a**, **14a-d** and trifluoroacetamides **10b**, **14e-f** have been studied by deuteration experiments with *n*-Bu₃SnD. The intramolecular hydrogen atom transfer from the N-alkyl side chain to the aryl radical takes place through competing 6-, 7-, 8-membered ring transition states.

Recently, we described¹ a method for the regioselective formation of C-centered radicals using an intramolecular 1,5-hydrogen atom transfer from a C(sp³)-H bond to an aryl radical.^{2,3} In the case of amines (and ethers) we have shown¹ that the naphthyl auxiliary introduced on the nitrogen favours the intramolecular 1,5-hydrogen atom transfer compared to the N-benzyl auxiliary (Scheme 1). In these experiments we could not detect any deuterium incorporation at C-2' or C-3' resulting from intramolecular 1,6- or 1,7-hydrogen atom transfers, respectively.⁴

Scheme 1



i = 1.1 eq. *n*-Bu₃SnH, 0.05 eq. AIBN, PhH (0.01 M), reflux.

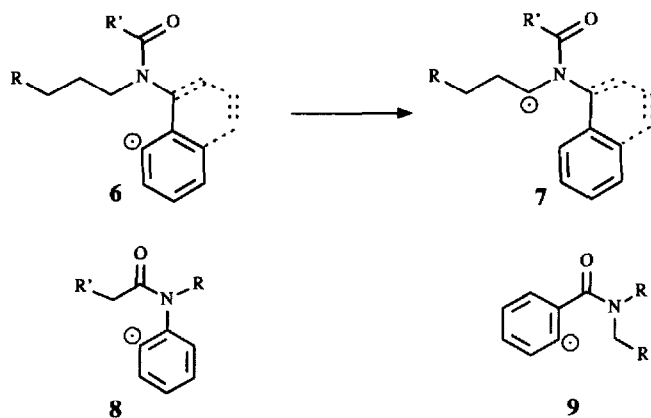
For the N-benzyl derivative **3** : **5** = 55 : 45; for the N-naphthyl derivative **3** : **5** = 16 : 84.

We decided to investigate the behaviour of the corresponding amides (**6**→**7**; Scheme 2), where the conformational freedom is further restricted due to the conjugation of the lone pair of the nitrogen with the carbonyl.

During our work, Snieckus^{3h} and Curran^{3h,1} reported the translocation reactions of the radicals **8** and **9** (Scheme

2). In these systems (**8,9**) the intramolecular 1,5- hydrogen atom transfer is possible only in the rotamers depicted in Scheme 2. The initial aryl radicals are reduced by $n\text{-Bu}_3\text{SnH}$ prior to rotation of the amide bond. No intramolecular 1,6- or 1,7-hydrogen atom transfer has been observed in **8,9**.^{3h,i} In contrast, in our systems both rotamers around the amide bond can undergo intramolecular hydrogen abstraction.

Scheme 2

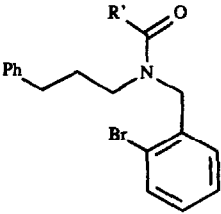
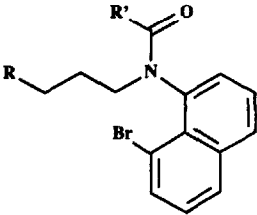
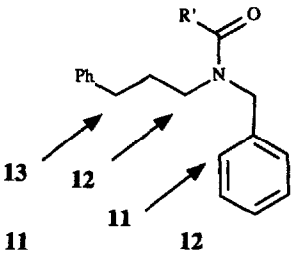
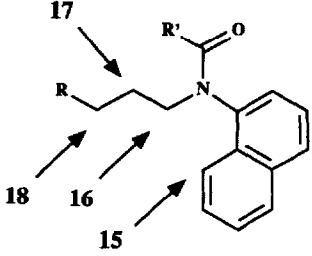


The treatment of the amides **10** under standard reaction conditions^{5,6} with $n\text{-Bu}_3\text{SnD}$ furnished not only the two expected deuterated compounds **11** and **12** resulting from the reduction of the initial aryl radical and from the intramolecular 1,5-hydrogen atom transfer, respectively (Table; entries 1,2). Their ratio (**11a** : **12a** = 6 : 7) parallels almost the one obtained in the case of the corresponding amine (Scheme 1). However, an identical amount of deuteration at C-3', arising from an intramolecular 1,7-hydrogen atom transfer, was detected (**13**; entries 1,2). No deuteration at C-2' was found.

In the corresponding naphthyl derivative **14a**, where the conformational freedom is even more restricted than in **10**, the deuteration occurred mainly at C-3' (64%; entry 3). This very high proportion of intramolecular 1,7-hydrogen atom transfer was unexpected.^{4,8} We have verified that this deuteration at C-3' arose from an intramolecular radical process and not from an intermolecular abstraction of the activated benzylic hydrogen. Indeed, the same ratio of deuteration at C-1' and C-3' was observed when the reaction was performed under different concentrations (0.05 M; 0.01 M; 0.002 M). Moreover, similar product distribution was obtained with a nitrile as C-3'-substituent (entry 4). These results suggest that, due to conformational restrictions introduced by the amide and the naphthyl groups, the eight-membered transition state for the radical translocation is energetically accessible. The hydrogen atom transfer readily takes place when the transition state is reached because of the activation of the C-3'-H bond towards homolysis by the phenyl (in **14a**) or the nitrile (in **14b**) substituents. Consequently, a decrease of the activation of the C-3'-H bond would lead to a decrease in deuteration of this position. This, exactly, was observed in the case of **14c** with the OMe substituent which is substantially less efficient in radical stabilization⁹ than the phenyl and the nitrile groups. In addition, no 1,7-hydrogen atom transfer was detected without substituent at C-3' (entry 6). For the same reasons, the two remaining competing intramolecular processes, namely the 1,5- and, to a minor extent, the 1,6-hydrogen atom transfer, were favoured. Houk¹⁰ postulated, based on *ab initio* molecular orbital calculations, that the intramolecular hydrogen atom transfer through a 7-membered ring transition state would have a lower activation enthalpy but a higher activation entropy compared to a 6-membered ring. Abundant literature precedents¹⁻³ are documenting the preference of the 1,5-hydrogen atom transfer versus the 1,6- and 1,7-process due to the lower activation entropy of the former pathway. However, in our systems **10** and especially **14** this

entropical term could be less critical as a result of the conformational restrictions introduced by the amide and naphthyl units. A similar trend was observed with the trifluoroacetamides **10b**, **14e**, **14f** (entries 2,7,8). In the reaction of **14e** and **14f** the 1,6- and the 1,7-transfers were even more favoured than in the corresponding acetamides **14a** and **14d**. In all these reactions we have never detected any deuteration at the methyl group adjacent to the amide function. This intramolecular 1,6-hydrogen atom transfer could only occur in the syn rotamer around the amide bond when the naphthyl radical is oriented towards the methyl group. These geometrical restrictions are probably responsible for this lack of deuteration α to the amide group.

Table. Extent of Intramolecular Hydrogen Atom Transfer

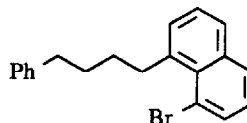
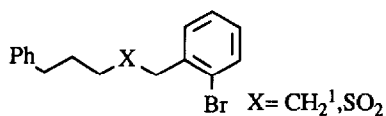
Entry	Radical Precursor	Product Distribution ⁶ [%]			Yield ⁷ [%]	
						
1	10a R' = CH ₃	30	35	35	96	
2	10b R' = CF ₃	38	31	31	96	
3	14a R = Ph R' = Me	4	n.d.	64	85	
4	14b R = CN R' = Me	n.d.	36	n.d.	83	
5	14c R = OMe R' = Me	n.d.	65	16	96	
6	14d R = H R' = Me	n.d.	80	20	n.d.	75
7	14e R = Ph R' = CF ₃	n.d.	17	5	78	80
8	14f R = H R' = CF ₃	20	40	30	10	66

The total amount of the intramolecular hydrogen atom transfers is higher in the naphthyl derivatives **14** than in the benzylic ones **10**. This is in agreement with our previous experiments on ethers and amines.¹ The reduced degree of freedom introduced by the linkage between the heteroatom and the naphthyl moiety increases the probability of the intramolecular hydrogen abstraction.

Although the amide auxiliaries **8,9** are very useful for the regioselective formation of the C-centered radicals^{3h,i}, competing intramolecular processes can take place in our isomeric systems **10, 14** due to different conformational restrictions.

REFERENCES AND NOTES

1. D. Denenmark, P. Hoffmann, T. Winkler, A. Waldner, A. De Mesmaeker, *Synlett*, **1991**, 621.
2. For the use of bromobenzyl auxiliary for the formation of α -alkoxy radicals see D.P. Curran, D. Kim, H.T. Liu, W. Shen, *J. Am. Chem. Soc.*, **1988**, *110*, 5900.
3. For further examples of intramolecular 1,5-hydrogen atom transfer in the presence of n-Bu₃SnH see a) A. De Mesmaeker, P. Hoffmann, B. Ernst, P. Hug, T. Winkler, *Tetrahedron Lett.*, **1989**, *30*, 6307 and 6311; b) A. De Mesmaeker, A. Waldner, P. Hoffmann, P. Hug, T. Winkler, *Synlett*, in press; c) A.L.J. Beckwith, D.M. O'Shea, S. Gerba, S.W. Westwood, *J. Chem. Soc., Chem Commun.*, **1987**, 666; d) J.K. Choi, D.J. Hart, *Tetrahedron*, **1985**, *41*, 3959; e) S.M. Bennet, D.L.J. Clive, *J. Chem. Soc., Chem. Commun.*, **1986**, 878; f) B. Chenera, C.P. Chuang, D.J. Hart, L.Y.Hsu, *J. Org. Chem.*, **1985**, *50*, 5409; g) D.C. Lathbury, P.J. Parsons, I. Pinto, *J. Chem. Soc., Chem. Commun.*, **1988**, 81; h) V. Snieckus, J.-C. Cuevas, C.P. Sloan, H. Liu, D.P. Curran, *J. Am. Chem. Soc.*, **1990**, *112*, 896; i) D.P. Curran, A.C. Abraham, H. Liu, *J. Org. Chem.*, **1991**, *56*, 4335; j) A.D. Borthwick, S. Caddick, P.J. Parsons, *Tetrahedron Lett.*, **1990**, *31*, 911; k) I. Rochigneux, M.-L. Fontanel, J.-C. Malanda, A. Doutheau, *Tetrahedron Lett.*, **1991**, *32*, 2017; l) see also B. Giese, J. Dupuis, T. Hasskerl, J. Meixner, *Tetrahedron Lett.*, **1983**, *24*, 703.
4. Few examples of intramolecular 1,6- and 1,7-hydrogen atom transfer in the presence of n-Bu₃SnH have been reported: a) A.L.J. Beckwith, D.R. Boate, *J. Chem. Soc., Chem. Commun.*, **1985**, 797; b) reference 3c. See also S.H. Pines, R.M. Purick, R. A. Reamer, G. Gal, *J. Org. Chem.*, **1978**, *43*, 1337.
5. All the reactions were performed by mixing the reagents at once in benzene (0.01 M) according to Scheme 1.
6. The isomer ratios were determined by ¹H-NMR (500 MHz) on the crude reaction mixtures. The deuterium content > 95% was verified by mass spectral analysis. In some cases the position of deuterium was also established by ¹³C-NMR (isotope effect and coupling).
7. The yields given in the Table refer to combined isolated yields after purification by flash chromatography on silica gel; n.d. = not detected.
8. However, the translocation of this type of radicals through seven- or eight-membered ring transition states is not restricted to amides. We have also detected products of deuteration resulting from intramolecular 1,6- and 1,7-hydrogen atom transfer in the following cases.



9. For a relative radical stabilization scale see R. Merenyi, Z. Janousek, H.G. Viehe in H.G. Viehe et al., "Substituent Effects in Radical Chemistry", D. Reidel Publishing Co., **1986**, 301.
10. A.E. Dorigo, K.N. Houk, *J. Am. Chem. Soc.*, **1987**, *109*, 2195.

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