AROMATIC CYCLIZATIONS OF β-AMINOETHYL RADICALS AND α-CARBAMOYLMETHYL RADICALS. ORTHO-SUBSTITUTION VS. IPSO-SUBSTITUTION

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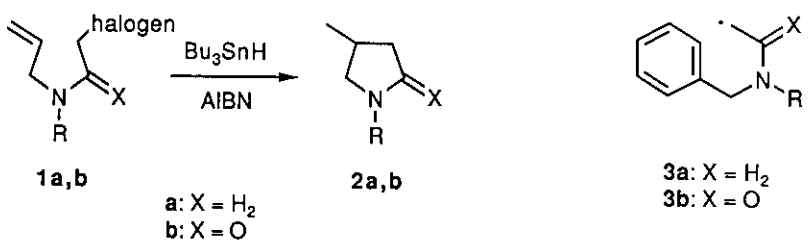
Abstract —— On being treated with Bu_3SnH, the N-benzyl-N-(β-bromoethyl)sulfonamide (**4**) underwent a homolytic ortho-substitution reaction to give the tetrahydroisoquinoline (**6**). In contrast, the N-arylmethyl-α-chloroacetamides (**10**) afforded the ipso-substitution products (**11**). A similar treatment of the N-naphthylmethyl derivative (**16**) provided the spiro-γ-lactam (**17**).

Considerable attention has recently been directed towards the synthesis of nitrogen-containing heterocycles by using radical cyclizations. The Bu_3SnH mediated cyclizations of the N-allylic β-haloethylamines (**1a**, $X=H_2$)[1] and the corresponding α-haloacetamides (**1b**, X=O),[2] which gave the five-membered products (**2a**) and (**2b**), respectively, have been extensively investigated. Our interest in this area has now been focused on the case where an aromatic ring serves as a radical acceptor in place of the olefinic double bond of **1a,b**. In this communication we wish to report the highly contrasting feature of the cyclization between the β-aminoethyl radicals (**3a**, $X=H_2$) and the α-carbamoylmethyl radicals (**3b**, X=O).



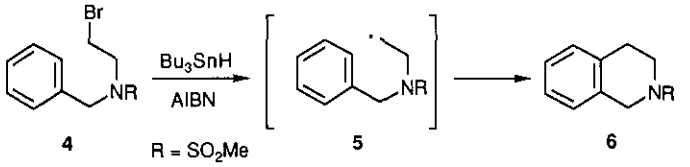
1a,b

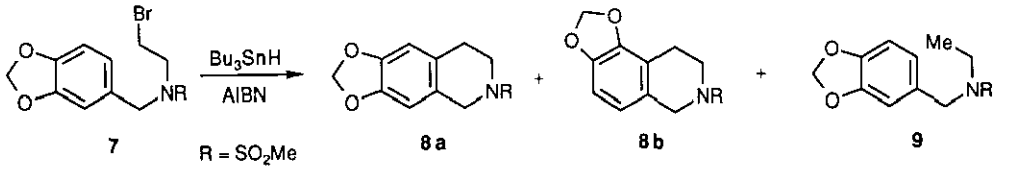
a: $X = H_2$
b: X = O

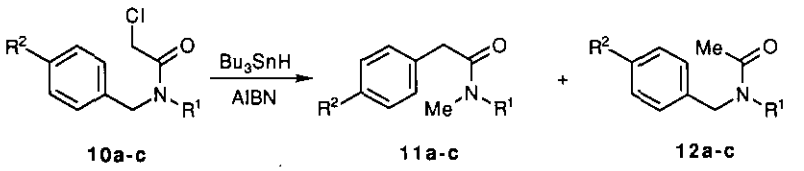
2a,b

3a: $X = H_2$
3b: X = O

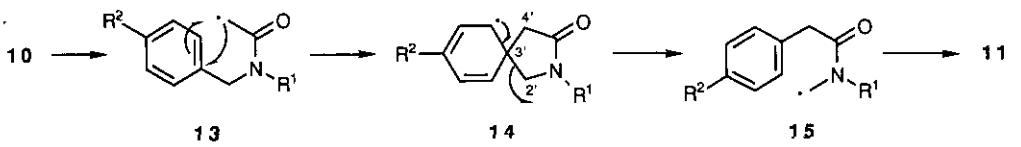
When the N-benzyl-N-(β-bromoethyl)sulfonamide (**4**) was treated with Bu_3SnH (1.1 eq.) and AIBN (0.1 eq.) in boiling toluene under high dilution conditions (10^{-4} M), the tetrahydroisoquinoline (**6**)[3] was obtained in 33% yield along with a small quantity of unidentified products. Similarly, the 3,4-methylenedioxyphenyl derivative (**7**) gave a mixture of **8a** and **8b**[4] (1.3:1) in 29% total yield together with the reduction product (**9**) (17%). The formation of **6** and **8a,b** can be rationalized in terms of an intramolecular ortho-substitution reaction of the β-aminoethyl radicals such as **5**. In contrast, N-benzyl-N-methyl-α-chloroacetamide (**10a**)[5] afforded the 1,4-aryl migration product (**11a**) in 12% yield along with the reduction product (**12a**) (73%). The N-cyclohexyl congeners (**10b**) and (**10c**) afforded **11b** and **11c** in 31 and 30% yields along with **12b** (40%) and **12c** (27%), respectively. The structures of **11a-c** were confirmed by direct comparison with authentic samples prepared from the corresponding arylacetic acid and amines.





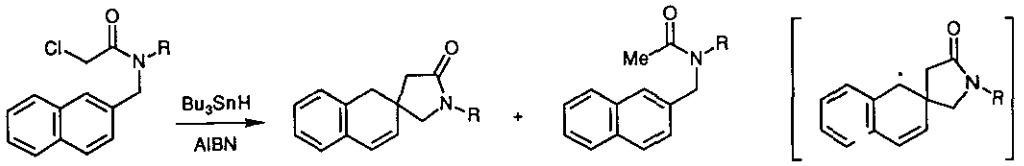


a: R^1 = Me, R^2 = H
b: R^1 = cyclohexyl, R^2 = H
c: R^1 = cyclohexyl, R^2 = OMe



A mechanistic rationalization of the formation of **11** from **10** involves an intramolecular ipso-attack of the radical intermediate (**13**) on the aromatic ring to give the spiro radical (**14**). This step is then followed by C(2')-C(3') bond cleavage, with concomitant aromatization, to give the α-acylamino radical (**15**), which is subsequently reduced by Bu_3SnH to afford **11**. In view of the general behavior of 4-arylbutyl radicals which undergo an ortho-substitution reaction to give the six-membered products even in the case where a carbonyl group is incorporated into the side chain,[6] it is somewhat surprising that the carbamoylmethyl radicals (**13**) underwent an ipso-substitution reaction to give the rearranged products (**11**). It should be also noted that this reaction is a first example of the homolytic aromatic ipso-substitution reaction in which the carbon atom acts as a leaving group. Other reported homolytic ipso-substitution reactions usually occurred at the ring carbon carrying a sulfonyl group or a halogen atom.[7] In the present instance, the formation of the stable α-acylamino radical (**15**) from **14** would play a crucial role in effecting the reaction.

Our attention was next turned to the N-naphthylmethyl derivative (**16**) in the hope that such radical intermediate as **19** might be trapped by Bu_3SnH. Thus, treatment of **16** with Bu_3SnH provided the spiro-γ-lactam (**17**)[8] in 45% yield along with the reduction product (**18**) (23%). No 1,4-aryl migration product was detected in the crude reaction mixture. The success of the isolation of **17** in good yield may be ascribed to the olefinic character of the C(1)-C(2) bond of the naphthalene ring or the benzylic stabilization of the newly formed radical intermediate (**19**).



In summary, our studies revealed that the β-aminoethyl radicals (**3a**, $X=H_2$) cyclize at the ortho-position to give six-membered products, whereas the α-carbamoylmethyl radicals (**3b**, X=O) attack on the ipso-position to lead to the formation of 1,4-aryl migration products or a spiro-γ-lactam. Although the exact reason for the difference in the mode of cyclization between **3a** and **3b** still remains obscure, it may reflect the geometric constrains and the stability of the initially formed radicals (**3**).

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1) A. Padwa, H. Nimmesgern, and G. S. K. Wong, J. Org. Chem., 1985, **50**, 5620; Y. Watanabe, Y. Ueno, C. Tanaka, M. Okawara, and T. Endo, Tetrahedron Lett., 1987, **28**, 3953; H. Urbach and R. Henning, Heterocycles, 1989, **28**, 957; D. L. J. Clive and A. Y. Mohammed, ibid., 1989, **28**, 1157; P. F. Keusenkothen and M. B. Smith, Tetrahedron Lett., 1989, **30**, 3369.

2) T. Sato, Y. Wada, M. Nishimoto, H. Ishibashi, and M. Ikeda, J. Chem. Soc., Perkin Trans. 1, 1989, 879; H. Ishibashi, T. S. So, T. Sato, K. Kuroda, and M. Ikeda, J. Chem. Soc., Chem. Commun., 1989, 762; G. Stork and R. Mah, Heterocycles, 1989, **28**, 723; J. M. Clough, G. Pattenden, and P. G. Wight, Tetrahedron Lett., 1989, **30**, 7469.

3) **6**: ^{1}H-Nmr (δ, ppm, $CDCl_3$, 60 MHz) 2.83 (3H, s), 3.00 (2H, br t, J=6 Hz), 3.59 (2H, br t, J=6 Hz), 4.47 (2H, s), 7.1-7.5 (4H, m).

4) **8a**: ^{1}H-Nmr (δ, ppm, $CDCl_3$, 300 MHz) 2.82 (3H, s), 2.87 (2H, t, J=5.9 Hz), 3.52 (2H, t, J=5.9 Hz), 4.34 (2H, s), 5.92 (2H, s), 6.54 (1H, s), 6.60 (1H, s). **8b**: 2.83 (3H, s), 2.87 (2H, t, J=5.9 Hz), 3.56 (2H, t, J=5.9 Hz), 4.40 (2H, s), 5.97 (2H, s), 6.58 (1H, d, J=8.0 Hz), 6.69 (1H, d, J=8.0 Hz).

5) In general, the corresponding bromoacetamides gave essentially the same distribution of the products.

6) M. Julia and J.-C. Chottard, Bull. Soc. Chim. Fr., 1968, 3691; E. I. Heiba and R. M. Dessau, J. Am. Chem. Soc., 1972, **94**, 2888; B. B. Snider, R. Mohan, and S. A. Kates, J. Org. Chem., 1985, **50**, 3659; G. A. Russel, B. H. Kim, and S. V. Kulkarni, ibid, 1989, **54** 3768.

7) For a review of homolytic aromatic ipso-substitution reactions, see: J. G. Traynham, Chem. Rev., 1979, **79**, 323. See also J. J. Kohler and W. N. Speckamp, Tetrahedron Lett., 1977, 631; D. L. J. Clive and T. L. B. Boivin, J. Org. Chem., 1989, **54**, 1997.

8) **17**: Ir (ν, cm^{-1}, CCl_4) 1690; ^{1}H-nmr (δ, ppm, $CDCl_3$, 300 MHz) 1.2-1.5 (4H, m), 1.6-1.9 (6H, m), 2.40, 2.46 (1H each, AB q, J=16.5 Hz), 2.87 (2H, s), 3.16, 3.26 (1H each, AB q, J=10.0 Hz), 3.97 (1H, double t, J=11.7, 3.7 Hz), 5.87 (1H, d, J=9.5 Hz), 6.49 (1H, d, J=9.5 Hz), 7.05-7.25 (4H, m).

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