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$_3$SnH, 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$_3$SnH mediated cyclizations of the N-allylic β-haloethylamines (1a, X=H$_2$) and the corresponding α-haloacetamides (1b, X=O), 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).

\[
\begin{array}{ccc}
1a,b & \xrightarrow{\text{Bu}_3\text{SnH}} & 2a,b \\
\& \text{halogen} & & \text{AIBN} \\
\end{array}
\]
When the \( \text{N-benzyl-N-(B-bromoethyl)sulfonamide (4)} \) was treated with \( \text{Bu}_3\text{SnH (1.1 eq.) and AIBN (0.1 eq.) in boiling toluene under high dilution conditions (10}^{-4} \text{ M)} \), 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 \( \beta \)-aminoethyl radicals such as 5. In contrast, \( \text{N-benzyl-N-methyl-\( \alpha \)-chloroacetamide (10a)} \)\(^5\) afforded the 1,4-aryl migration product (11a) in 12% yield along with the reduction product (12a) (73%). The \( \text{N-cyclohexyl congeners (10b) and (10c)} \) 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.

\[
\begin{align*}
\text{Br} & \quad \text{Bu}_3\text{SnH} \\
\text{AIBN} & \quad \text{R} = \text{SO}_2\text{Me} \\
\end{align*}
\]

\[
\begin{align*}
\text{Br} & \quad \text{Bu}_3\text{SnH} \\
\text{AIBN} & \quad \text{R} = \text{SO}_2\text{Me} \\
\end{align*}
\]

\[
\begin{align*}
\text{Cl} & \quad \text{Bu}_3\text{SnH} \\
\text{AIBN} & \quad \text{R}^1 = \text{Me, R}^2 = \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 & \quad \text{Bu}_3\text{SnH} \\
\text{AIBN} & \quad \text{R}^1 = \text{cyclohexyl, R}^2 = \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 & \quad \text{Bu}_3\text{SnH} \\
\text{AIBN} & \quad \text{R}^1 = \text{cyclohexyl, R}^2 = \text{OMe} \\
\end{align*}
\]
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 Bu₃SnH 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, 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. 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 Bu₃SnH. Thus, treatment of 16 with Bu₃SnH provided the spiro-γ-lactam (17) 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=H₂) 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).
REFERENCES AND NOTES


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.


8) 17: Ir (v, 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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