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3,6-Dihydropyridines from 6-*endo* Radical Cyclisation onto Nitrogen in β-Allenyl Ketoximebenzoates

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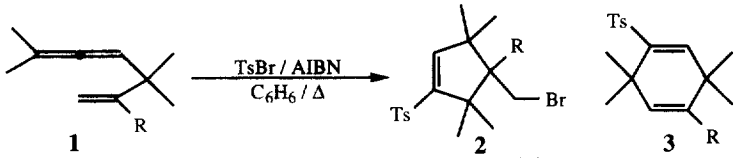
Abstract: When tosyl bromide is added under free radical conditions to β-allenyl-1-phenylketoximebenzoates, a carbon-centred radical resulting from the addition of the tosyl radical on the sp carbon is formed. Depending on the substitution pattern of the allenyl moiety, this carbon-centred radical traps a bromine atom or undergoes a rare 6-*endo* cyclisation onto the nitrogen atom leading to 3,6-dihydropyridines in good yields.

As we have previously reported,[1] radical additions to allene derivatives having in β-position a radical acceptor such as carbon-carbon or carbon-nitrogen double bond have been useful methods for building highly functionalized cyclopentenes or cyclohexenes. We have particularly shown that the tosyl[2] mediated radical cyclisation of the allylallenes **1** led to the cyclised compounds **2** and **3** in a ratio which is conditioned by the R substituent steric hindrance[1d, 3] as it is normally expected.[4]



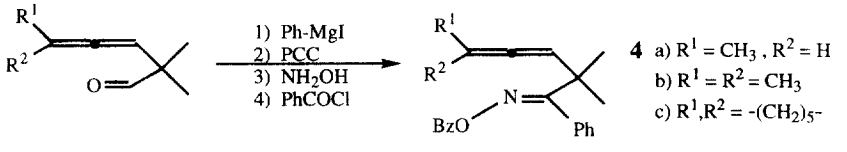
1
a) R = H
b) R = CH_3
c) R = C_6H_5

2
a) 82%
b) 35%
c) 0%

3
a) 0%
b) 58%
c) 51%

Scheme 1

We now describe our results about the radical addition of tosyl bromide to the β-allenyl ketoximebenzoates **4a,b,c** which have been easily prepared in good yield[5] from the corresponding β-allenyl aldehydes according to the following scheme:



4 a) $R^1 = CH_3$, $R^2 = H$
b) $R^1 = R^2 = CH_3$
c) $R^1, R^2 = -(CH_2)_5-$

Scheme 2

The reaction of compounds **4** with tosyl bromide and AIBN in refluxing cyclohexane afforded the compounds **5** or **6**, **7**, and **8** depending on the substitution pattern of the allenyl moiety.[6]

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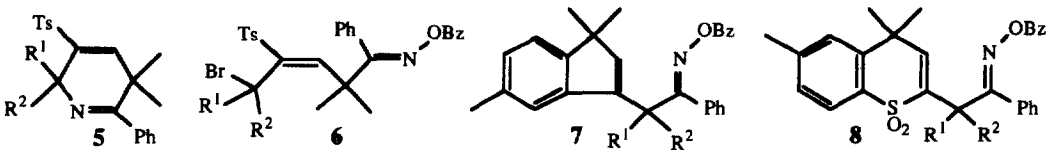


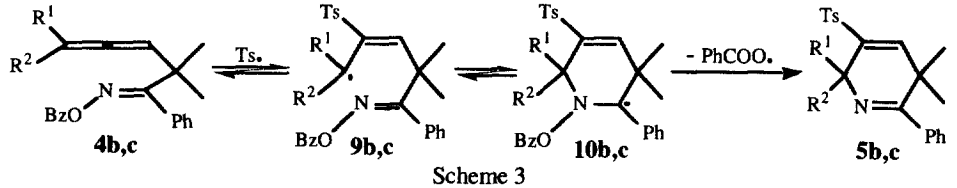
a) $R^1 = CH_3$, $R^2 = H$; b) $R^1 = R^2 = CH_3$; c) $R^1,R^2 = -(CH_2)_5-$

starting material	compound (%)	% of recovered **4**
4a	**6a** (38) **7a** (8) **8a** (6)	27
4b	**5b** (94)	0
4c	**5c** (42)	18

Starting from **4b,c** the reaction gave the cyclised compounds **5b,c** as the sole product. Starting from **4a** three products (**6a**, **7a**, **8a**) were obtained.

The structure of compound **5b**† has been determined by X-ray structural analysis; all the compounds were fully characterised by ^1H and ^{13}C NMR, MS and elemental analysis. As we did not succeed in separating **7a** and **8a**, their structures were analysed from the mixture using 2D NMR experiments. In this way we have established unambiguously the structure of **7a** while the attribution of chemical shifts for **8a** is not complete.

Compounds **5b,c** arise from a 6-*endo-trig* cyclisation involving the C centred radicals **9b,c** early formed by the addition of the tosyl radical on the sp allenic carbon. This cyclisation leads to the new radicals **10b,c** which lose a benzoyl radical to afford **5b,c**.



Scheme 3

To our knowledge, no example of such a process has been reported in the literature about oxime derivatives. However, cyclisations of C radicals onto imine N-atom have been described.[7] These works show that 6-*endo* radical cyclisations onto the nitrogen atom are scarce and poorly efficient. In this context the very selective formation of **5b,c** seems to be quite surprising. At first glance, this excellent regioselectivity of the cyclisation could be attributed to the stabilisation of the *endo*-radical **10b,c** by the phenyl group. On further examination, semi-empirical calculations[8] have shown that the conformation of **10b** with the phenyl group non conjugated with the single occupied molecular orbital is 23 $kJ.mol^{-1}$ more stable than the conformation with the phenyl group conjugated because of high steric hindrance caused by the two neighbouring methyl substituents. Thus stabilisation of radicals **10b,c** by electronic π delocalisation does undoubtedly not occur. In addition, the examination of structures, obtained by X-ray crystal analysis, of both compounds **4b**† and **5b** shows clearly that the phenyl ring is not in plane with the C=N double bond but perpendicular.

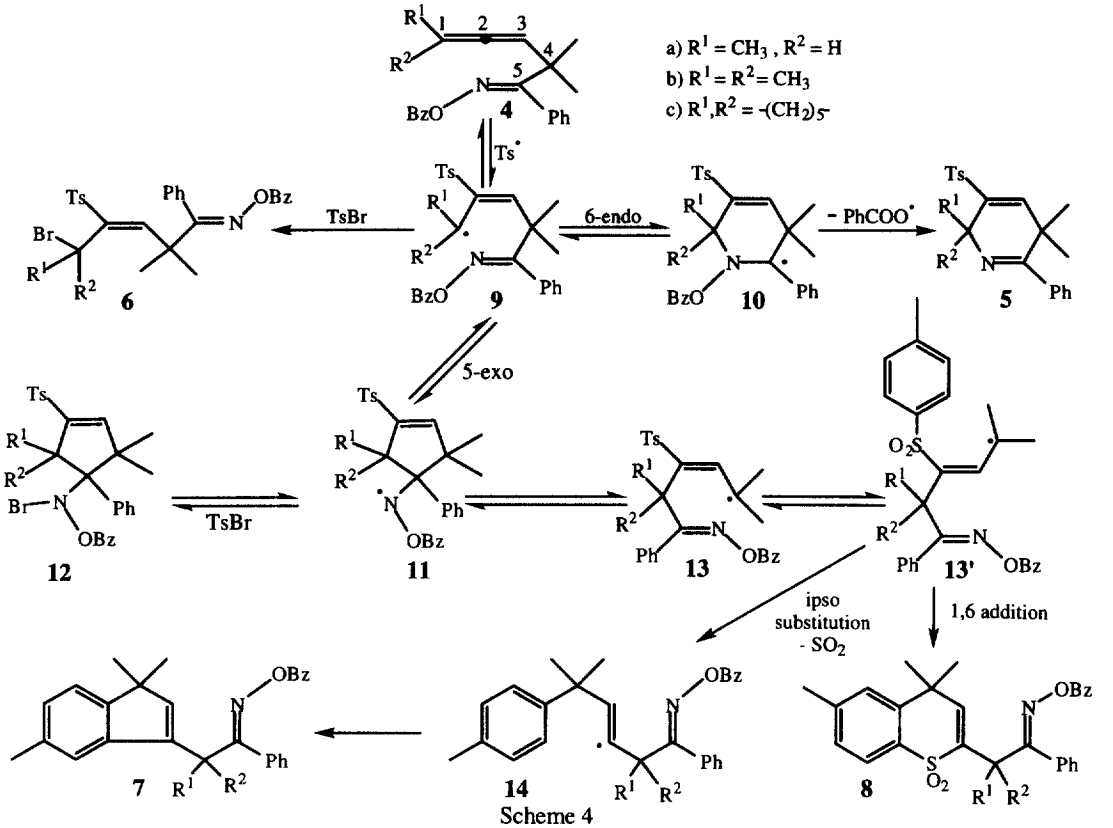
The scheme 4 is an attempt to rationalize all our results. Starting from **4b,c** the regioselectivity observed in the formation of **5b,c** from **9b,c** seems to be governed by steric factors according to Beckwith's guideline.[4]

Starting from **4a**, the formation of **6a** as major product and the obtaining of **7a** and **8a** deserve some comments. The radical **9a** proceeding from the first step of the reaction has three possible pathways:

† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW.

1) This radical traps a bromine from TsBr leading to **6a** as the major product of the reaction. This can be explained by the fact that the steric hindrance at the C-1 position is lower in **9a** than in **9b,c**.

2) Like **9b,c**, it may undergo a 6-*endo* cyclisation leading so to the dihydropyridine **5a**. As **5a** was not detected in the crude mixture, that does not seem to be a favoured pathway.



Scheme 4

3) 5-*exo* cyclisations onto a carbon-nitrogen double bond are more rapid than on alkenes[7] as well for stereoelectronic effects as for the carbon-nitrogen bond polarisation.[9] So, due to its less hindered C-1 position, the radical **9a** may also undergo a 5-*exo* cyclisation although the C-5 position is hindered by the phenyl group. The feasibility of such a process has been shown by using tributyltin hydride instead of tosyl bromide.[10] But this tosyl-mediated 5-*exo* cyclisation would result in the N-bromo amine **12a** which is probably reversiblely formed in our conditions.[11] In addition, the aminyl radical **11a** reversiblely formed from **9a** may undergo an other β-fission leading to **13a**. Based on these considerations we can explain the formation of the compounds **7a** and **8a**. The isomerisation of the allyl radical[12] **13a** gives **13a'** which may act at the aromatic ring of the arenesulfonyl group in two competing pathways supported by some examples taken in the literature.[13]

(a) [1,5] *ipso* substitution with subsequent loss of sulphur dioxyde leads to the vinyl radical **14** which adds to the aromatic ring affording compound **7a**. (b) Direct [1,6] addition leads to compound **8a**.

In summary, we showed that, starting from β-allenyl ketoximes **4**, the functionalized 3,6-dihydropyridines **5** can be obtained in fairly good yields depending on the substitution pattern on the allenyl moiety.

References and Notes

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5. All compounds have NMR (^1H, ^{13}C) data and combustion analysis in agreement with the structures assigned. Selected spectroscopic data for **4b**: White needles, m.p. 104-106°C; ^1H NMR ($CDCl_3$, TMS, 200 MHz) δ 1.38 (s, 6H), 1.59 (d, 2.8 Hz, 6H), 5.12 (heptet, 2.8 Hz, 1H), 7.15 - 7.60 (m, 10H); ^{13}C NMR ($CDCl_3$, TMS, 50 MHz) δ 201.37 (C), 174.01 (C), 163.74 (C), 133.55 (C), 132.92 (CH), 129.41 (CH), 129.18 (C), 128.31 (CH), 128.25 (CH), 127.70 (CH), 127.25 (CH), 98.71 (C), 96.20 (CH), 42.67 (C), 26.08 (CH_3), 20.25 (CH_3); *Anal.* Calcd. for $C_{22}H_{23}NO_2$ C: 79.25, H: 6.95, N: 4.20; Found C: 79.18, H: 6.95, N: 4.12.
6. In a typical experiment a 0.02 M cyclohexane solution of the oxime benzoate **4** was refluxed with TsBr (1.5 eq) and AIBN (0.2 eq). The reaction, monitored by TLC, was completed in 2.5 hours for **4b**, and stopped after 24 hours for **4a** and **4c**. After evaporation of the solvent, the crude product was purified by flash chromatography over silicagel. Starting from **4a** only the compound **6a** has been isolated; the isomeric ratio of **7a** and **8a** was determined by the ^1H NMR spectrum integration of the mixture. Selected spectroscopic data: Compound **6a**: White crystals, m.p. 146-147°C; ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ 1.54 (s, 3H), 1.61 (s, 3H), 1.93 (d, 7.1 Hz, 3H), 2.44 (s, 3H), 5.73 (q, 7.1 Hz, 1H), 7.05 - 7.08 (m, 2H), 7.07 (s, 1H), 7.24 - 7.45 (m, 8H), 7.57 - 7.59 (m, 2H), 7.82 - 7.84 (m, 2H); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 170.90 (C), 163.24 (C), 148.12 (CH), 145.78 (C), 144.38 (C), 138.85 (C), 133.25 (CH), 132.30 (C), 129.74 (CH), 129.47 (CH), 129.19 (CH), 128.56 (C), 128.42 (CH), 128.39 (CH), 128.36 (CH), 127.00 (CH), 43.62 (C), 38.20 (CH), 28.05 (CH_3), 27.51 (CH_3), 24.21 (CH_3), 21.71 (CH_3); *Anal.* Calcd. for $C_{28}H_{28}NO_4SBr$ C: 60.65, H: 5.09, N: 2.53; Found C: 60.61, H: 5.17, N: 2.50. Compound **5b**: White crystals, m.p. 110-112°C; ^1H NMR ($CDCl_3$, TMS, 200 MHz) δ 1.30 (s, 6H), 1.44 (s, 6H), 2.41 (s, 3H), 6.90 (s, 1H), 7.28 - 7.34 and 7.73 - 7.78 (2m, 9H); ^{13}C NMR ($CDCl_3$, TMS, 50 MHz) δ 168.00 (C), 144.46 (CH), 144.19 (C), 144.02 (C), 139.33 (C), 138.62 (C), 129.73 (CH), 128.26 (CH), 128.07 (CH), 127.79 (CH), 127.65 (CH), 58.23 (C), 38.39 (C), 29.93 (CH_3), 27.47 (CH_3), 21.55 (CH_3); *Anal.* Calcd. for $C_{22}H_{25}NO_2S$ C: 71.90, H: 6.86, N: 3.81; Found C: 71.82, H: 6.78, N: 3.86.
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