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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. © 1999 Published by Elsevier Science Ltd. All rights reserved.

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 tosyl² 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



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 yield⁵ from the corresponding β -allenyl aldehydes according to the following scheme:



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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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 $5b^{\dagger}$ has been determined by X-ray structural analysis; all the compounds were fully characterised by ¹H and ¹³C 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.



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 calculations⁸ 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.



3) 5-exo cyclisations onto a carbon-nitrogen double bond are more rapid than on alkenes⁷ 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 radical¹² **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 3,6dihydropyridines 5 can be obtained in fairly good yields depending on the substitution pattern on the allenyl moiety.

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- All compounds have NMR (¹H, ¹³C) data and combustion analysis in agreement with the structures assigned. Selected spectroscopic data for 4b: White needles, m.p. 104-106°C; ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (CH₃), 20.25 (CH₃); Anal. Calcd. for C₂₂H₂₃NO₂ 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 (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (CH₃), 27.51 (CH₃), 24.21 (CH₃), 21.71 (CH₃); Anal. Calcd. for C28H28NO4SBr 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 (CDCl₃, 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); ¹³C NMR (CDCl₃, TMS, 50 MHz) & 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 (CH₃), 27.47 (CH₃), 21.55 (CH₃); Anal. Calcd. for C22H25NO2S C: 71.90, H: 6.86, N: 3.81; Found C: 71.82, H: 6.78, N: 3.86.
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