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Radical cyclisation onto nitriles

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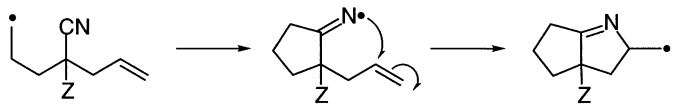
Abstract

Iminyl radicals, generated by 5-*exo* cyclisation of alkyl, vinyl and aryl *C*-centred radicals onto nitriles, undergo β-scission (nitrile translocation), reduction or tandem cyclisation onto alkenes depending on the nature of the α-substituent. 5-*exo* Cyclisations of aryl radicals onto nitriles undergo nitrile translocation when the α-substituent is CN, CO_2R, SO_2Ph or $CONMe_2$. The rate of translocation is faster than 5- or 6-*exo* cyclisation onto alkenes or 1,5-hydrogen abstraction of allylic hydrogens. When the α-substituents are alkyl, the intermediate iminyl radicals do not undergo nitrile translocation.

Keywords: radical cyclisation; nitriles; iminyl radicals; β-scission.

Radical cyclisation onto nitriles remains enigmatic[1] with both successes[2] and failures[3] reported. In our studies towards the synthesis of bicyclic nitrogen heterocycles we sought to use tandem radical reactions involving cyclisation onto nitriles to yield intermediate iminyl radicals followed by cyclisation of the iminyl radicals onto suitably placed alkenes (Scheme 1). Although this type of tandem reaction has not been previously reported, iminyl radicals generated by cyclisation onto nitriles have been shown to cyclise onto arenes by an oxidative mechanism.[4] The cyclisation of iminyl radicals onto alkenes has been studied by Zard[5] and reviewed.[1,5] The rate of cyclisation of 2-methyl-6,6-diphenyl-5-hexeniminyl has been measured[6] as 2.2×10^6 s^{-1} at 25°C. We report our initial results as a guide to further understanding the reactivity of radical cyclisation onto nitriles.



Scheme 1. Tandem cyclisation of iminyl radicals generated by cyclisation onto nitriles

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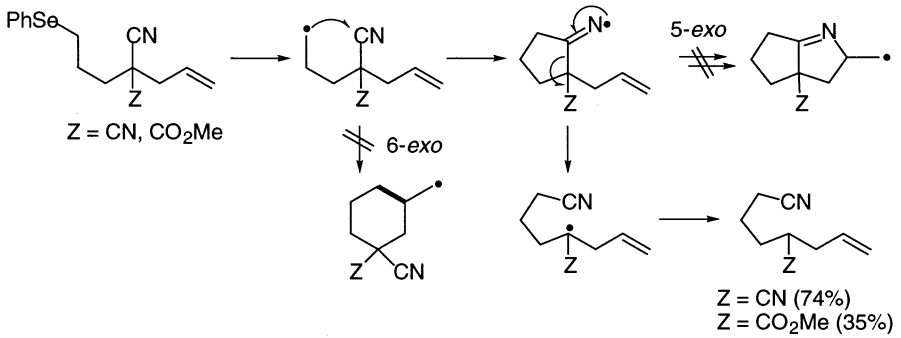
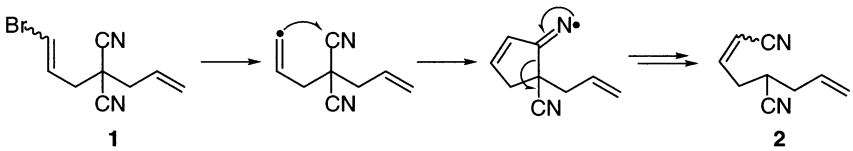
The use of radical cyclisation onto nitriles has been hindered by the slow rate and is not generally synthetically favourable, e.g. the rate of cyclisation of 5-cyanobutyl is 4×10^4 s^{-1} at 80°C.[7] In order to accelerate the rate of cyclisation of nucleophilic *C*-centred radicals onto nitriles we studied the radical cyclisation of precursors with electron withdrawing α-substituents (Scheme 2). We were mindful of the known radical translocation of nitriles facilitated by the stability of the nitrile triple bond. Reported examples indicate that these translocations are favoured by ring strain[8–10] and the formation of stabilised radicals.[9,11–14]



Scheme 2. Nitrile translocation via alkyl radical cyclisation. Bu_3SnH (1.3 equiv., syringe pump addition over 3 h), Z=CN (9 h reflux, AIBN, PhMe); $Z=CO_2Me$ (6 h, cyclohexane, AMBN)

The cyclisation was fast as predicted with no traces of 6-*exo* cyclisation onto the alkene, i.e. the rate of cyclisation onto the nitrile was faster than the rate of 6-*exo* cyclisation (4.1×10^4 s^{-1} at 80°C).[15] Both rates would be enhanced by Thorpe–Ingold effects because of the *gem*-disubstitution. The electron withdrawing effect of the α-substituent should increase the electrophilicity of the nitrile and the intermediate iminyl radical and therefore enhance both the rate of cyclisation onto the nitrile and of the iminyl radical onto the alkene. However, the rate of β-scission is clearly faster and no traces of tandem products were observed. In general the rate of cyclisation of iminyl radicals is one order of magnitude less rapid than the equivalent carbon radical,[6] i.e. ca. 2.5×10^4 s^{-1} indicating that the rate of nitrile translocation is reasonably fast even when little ring strain is present. GCMS analysis indicated near quantitative yields of translocated products and lower isolated yields reflect problems of separation from tin residues.

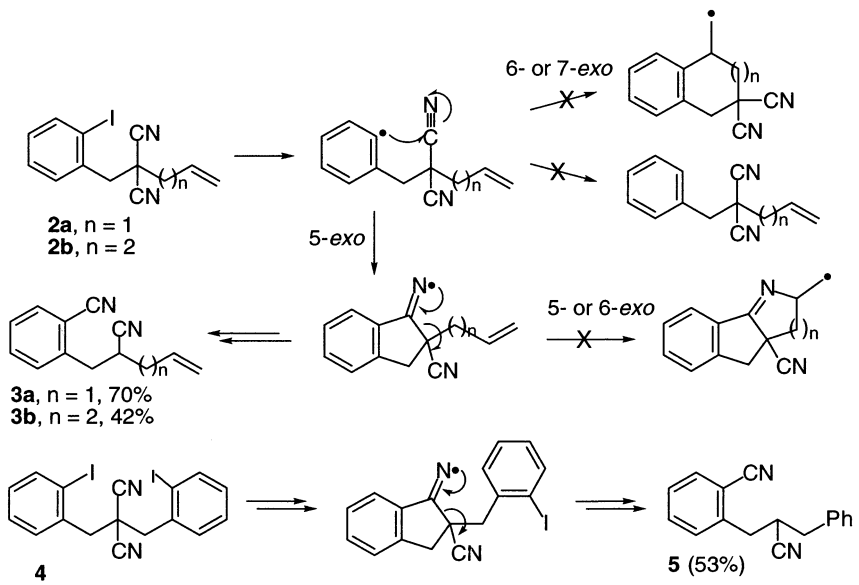
Similar translocation has been reported[12] for cyclisation of 4-cyano-4-(ethoxycarbonyl)-1-buten-1-yl radicals [$(EtO_2C)(CN)CHCH_2CH{=}CH^{\bullet}$]. Therefore, we also tested whether translocation was faster than 5-*exo* cyclisation of the intermediate iminyl radical with precursor **1** (Scheme 3). The vinyl bromide **1** also gave only nitrile translocation with the nitrile **2** as the only detectable product. After some difficulty of separation, **2** was isolated in 23% yield. Again, the rate of cyclisation onto the nitrile is faster than 6-*exo* cyclisation of the vinyl radical onto the



Scheme 3. Nitrile translocation via vinyl radical cyclisation. Bu_3SnH (1.3 equiv., syringe pump addition over 3 h), (6 h reflux, AMBN, cyclohexane)

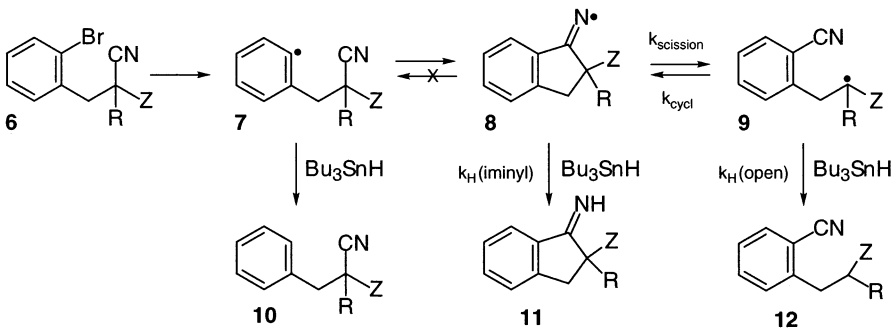
alkene and the rate of translocation is faster than 5-*exo* cyclisation of the iminyl radical onto the alkene.

The planned tandem cyclisation using aryl radicals from **2a** and **2b** also failed and only translocation (**3a** (70%) and **3b** (42%), respectively) in high yield (by GCMS) was detected (Scheme 4). Again, β-scission of the intermediate iminyl radicals was faster than cyclisation onto the pendant alkenes and no products resulting from 5- or 6-*exo* cyclisation or from 1,5-hydrogen abstraction of the allylic hydrogen in **2b** were observed. Similarly, only translocation (**5**, 53%) was obtained for precursor **4** and the possible 5-*exo* or 6-*endo* cyclisation onto the aryl ring was not observed.



Scheme 4. Nitrile translocation via aryl radical cyclisation. Bu_3SnH (1.3 equiv., syringe pump addition over 6 h), (9 h reflux, AMBN, cyclohexane)

We decided to use this system as a model for studying the effect of the α-substituent on translocation of the nitrile group and the results are shown in Scheme 5 and Table 1. When the α-substituent was an electron withdrawing group (CN, $CONMe_2$, CO_2Et, SO_2Ph) and phenyl, only translocation to **12** and no cyclised imine **11** was observed. When the α-substituent was an



Scheme 5. Effect of α-substituent on nitrile radical translocation

Table 1
Cyclisation of aryl radicals onto nitriles

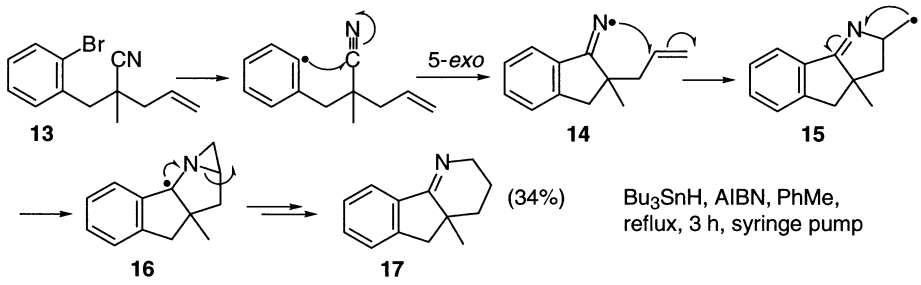
Precursor **6**	% yield **10**	% yield **11**	% yield **12**	Reaction conditions[a]
Z = CN, R = H	0	0	72	Cyclohexane, AMBN,[b] 9 h, syringe pump
Z = $CONMe_2$, R = H	7	0	41	Toluene, AIBN, 9 h, syringe pump
[10]Z = CO_2Et, R = H	12	0	59	
Z = Ph, R = H	5	0	24 (24[c])	Toluene, AIBN, 2 h[d]
Z = SO_2Ph, R = H	7	0	16	Toluene, AIBN, 2 h[d]
Z = *o*-BrBn, R = H	0	15[e]	0	Toluene, AIBN, 7 h, syringe pump
Z = Me, R = H	0	15[e]	0	Toluene, AIBN, 7 h, syringe pump
Z = Me, R = Me	0	57[e] (48[14])[e]	0	Toluene, AIBN, 7 h, syringe pump

[a] Bu_3SnH (1.3 equiv.), reflux, under nitrogen.
[b] AMBN (azobismethylisobutyronitrile, or 2-(1-cyano-1-methyl-propylazo)-2-methylbutyronitrile) was used because AIBN is insoluble in cyclohexane.
[c] 8,10-Dihydrophenanthrene-1-carbonitrile.
[d] All reagents added at the beginning of the reaction.
[e] Isolated as the corresponding ketone after hydrolysis of the imine.

electron donating group (alkyl, Bn), no translocation to **12** and only cyclised imine **11** (hydrolysed, as the respective ketone) was observed. For the latter group, the yields were poor except when disubstituted. The reactions for **6** (R = H, Z = SO_2Ph and Ph) were problematic and reactions using syringe pump addition of the Bu_3SnH were inhibited and gave only unaltered starting material. We suggest that this inhibition is caused by disproportionation between the intermediate aryl radical **7** and an intermediate biaryl π-radical, generated by addition of the initial nucleophilic aryl radical **7** to the electrophilic arene in the α-substituent in a bimolecular reaction.

We propose that the results are explained by the α-substituents, as shown in Scheme 5. When the α-substituent is electron withdrawing, the rate of β-scission is faster than trapping of the weakly nucleophilic iminyl radicals with Bu_3SnH. The equilibrium between intermediate iminyl radicals **8** and ring-opened radicals **9** is also aided by rapid reaction between the strongly electrophilic ring-opened radical **9** and the nucleophilic Bu_3SnH, i.e. $k_H(\text{open}) \gg k_H(\text{iminyl})$ and the slow rate of cyclisation between the electrophilic radical and the electrophilic carbon of the nitrile group. Weakening of the C–(C=N$^\bullet$) bond and stabilisation of the ring-opened radicals by the α electron withdrawing, and α-phenyl, groups also plays an important role. For α electron donating groups the rate of H-transfer between the nucleophilic Bu_3SnH and the weakly nucleophilic iminyl or ring-opened radicals will be similar and the rate of cyclisation by attack of the nucleophilic α-alkyl radical on the electrophilic centre of the nitrile will be faster than β-scission. Likewise, the weakening of the C–(C=N$^\bullet$) bond will be less than for electron-withdrawing groups. The literature reports conflicting results for α-(2-bromophenylamino)nitriles, which yield selective translocation[14a] or largely imine formation.[14b]

The conclusion is that tandem cyclisation will best be facilitated by use of α-alkyl substituents and initial study has shown this to be the case. The α-propenyl nitrile **13** readily gave tandem cyclisation to yield **17**, apparently by a 5-*exo*, 6-*endo* cyclisation, and small amounts (<5%) of the 5-*exo*, 5-*exo* tandem product (Scheme 6). We propose that the iminyl radical **14** undergoes a 5-*exo* cyclisation to **15** which undergoes rearrangement via the stable α-aminyl benzylic radical



Scheme 6. Tandem cyclisation via intermediate iminyl radicals

16 rather than 6-*endo* cyclisation. The tricycle **17** could also be arise from thermodynamic control of the second cyclisation, i.e. **14** to **15** is reversible. However, reversibility is unlikely because iminyl radicals (e.g. **14**) are not stabilised and thermodynamic control is only observed for stable radicals.

Our results have shown the further synthetic potential of radical cyclisation onto nitrile groups. Choice of the α-substituent can facilitate nitrile translocation, cyclisation to imines and tandem cyclisation of the intermediate iminyl radical.

Acknowledgements

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References

1. Review: Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543–17594.
2. Representative papers: Curran, D. P.; Liu, W. *Synlett* **1999**, 117–119; Yamamoto, Y.; Matsumi, D.; Itoh, K. *J. Chem. Soc., Chem. Commun.* **1998**, 875–876; Alonso, R. A.; Burgey, C. S.; Rao, B. V.; Vite, G. D.; Vollerthun, R.; Zottola, M. A.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1993**, *115*, 6666–6672 and references cited therein; Snider, B. B.; Buckman, B. O. *J. Org. Chem.* **1992**, *57*, 5322–5426; Clive, D. L.; Beaulieu.; Set, L. *J. Org. Chem.* **1984**, *49*, 1314–1316; Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821–2814; Molander, G. A.; Wolfe, C. N. *J. Org. Chem.* **1998**, *63*, 9031–9036.
3. Kilburn, J. *Tetrahedron Lett.* **1990**, *31*, 2193–2196; Yeung, B.-W. A.; Contelles, J. L. M.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1989**, 1160–1162; Chenera, B.; Chuang, C.-P.; Hart, D. J.; Hsu, L.-Y. *J. Org. Chem.* **1985**, *50*, 5409–5410.
4. Montevecchi, P. C.; Navacchia, M. L.; Spagnolo, P. *Tetrahedron* **1998**, *54*, 8207; Curran, D. P.; Liu, H.; Josien, H.; Ko, S.-B. *Tetrahedron* **1996**, *52*, 11385–11404; Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1991**, *113*, 2127–2132; Camaggi, C. M.; Leardini, R.; Nanni, D.; Zanardi, G. *Tetrahedron* **1998**, *54*, 5587–5598; Nanni, D.; Pareschi, P.; Rizzoli, C.; Sgarabotto, P.; Tundo, A. *Tetrahedron* **1995**, *51*, 9045–9062; Leardini, R.; Nanni, D.; Pareschi, P.; Tundo, A.; Zanardi, G. *J. Org. Chem.* **1997**, *62*, 8394–8395 and *Tetrahedron Lett.* **1998**, *39*, 2441–2442.
5. Review: Zard, S. Z. *Synlett* **1996**, 1148–1154.
6. Le Radic-Biadatti, M.-L.; Callier-Dublanchet, A.-C.; Horner, J. H.; Quiclet-Sire, B.; Zard, S. Z.; Newcomb, M. *J. Org. Chem.* **1997**, *62*, 559–563.
7. Griller, D.; Schmid, P.; Ingold, K. U. *Can. J. Chem.* **1979**, *57*, 831–833.

8. Quiclet-Sire, B.; Callier, A. C.; Zard, S. Z. *Tetrahedron Lett*. **1994**, *35*, 6109–6112; Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett*. **1997**, *38*, 2463–2466; Boivin, J.; Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Scaiano, A.-M.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 6517–6528;
9. Curran, D. P.; Seong, C. M. *Tetrahedron* **1992**, *48*, 2175–2190.
10. Boivin, J.; Fouquet, E.; Zard, S. Z. *Tetrahedron* **1994**, *50*, 1757–1768.
11. Kim, S.; Jon, S. Y. *J. Chem. Soc., Chem. Commun*. **1998**, 815–816.
12. Beckwith, A. L. J.; O'Shea, D. M.; Gerba, S.; Westwood, S. W. *J. Chem. Soc., Chem. Commun*. **1987**, 666–667; Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc*. **1988**, *110*, 2565–2575.
13. Rychnovsky, S. D.; Swenson, S. S. *Tetrahedron* **1997**, *53*, 16489–16502.
14. (a) Cossy, J.; Poitevin, C.; Pardo, D. G.; Peglion, J. L. *Synthesis* **1995**, 1368–1370; (b) Sulsky, R.; Gougoutas, J. Z.; DiMarco, J.; Biller, S. A. *J. Org. Chem*. **1999**, *64*, 5504–5510.
15. Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Chem. Commun*. **1974**, 472–473.