PERKIN 1 COMMUNICATION

Vinyl isonitriles in radical cascade reactions: formation of cyclopenta-fused pyridines and pyrazines

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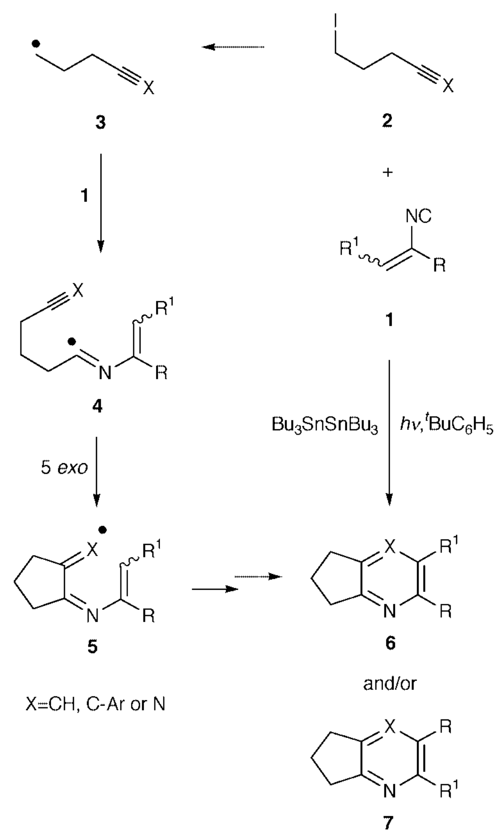
The 4 + 1 radical annulation reaction of vinyl isonitriles with iodoalkynes or iodonitriles affording cyclopenta-fused pyridines and pyrazines respectively and the first example of an intramolecular radical addition to an aryl isonitrile are described.

The application of tandem radical processes has proved to be both an effective and efficient approach for the preparation of a wide range of polycyclic molecules.[1] Recently, isonitriles have been utilized in tandem radical processes for the formation of a number of heterocyclic moieties.[2,3] Precursors to the antitumor agent campthothecin and related natural products have been prepared by such an approach.[4] The 4 + 1 radical annulation strategy adopted, involving intermolecular addition to the isonitrile and subsequent cyclisation, has, however, only been described with aromatic isonitriles. Herein we describe our efforts to further extend the scope of this methodology by utilizing vinylic isonitriles in place of aryl isonitriles as well as our initial investigations into the feasibility of tandem radical reactions in which addition to an isonitrile occurs in the intramolecular sense.

Four vinyl isonitriles **1a**–**d** were chosen for our study and prepared *via* trifluoromethanesulfonic anhydride mediated dehydration of the corresponding vinyl formamides in reasonable yield (66, 87, 93, and 46% respectively).[5] The vinyl formamides may themselves be readily prepared according to the methods of Baldwin or Barton from the corresponding thiooxime or oxime.[6,7] Vinyl isonitriles **1a**–**d** were treated with 5-iodopentyne **2a** at 150 °C and hexabutylditin (1.5 mmol) in *tert*-butylbenzene under sunlamp irradiation for 48 hours.[2,4] In each case a tetrasubstituted pyridine was obtained *via* the desired 4 + 1 annulation (Scheme 1 and Table 1) in 46–72% yield. Unfortunately, despite extensive studies we were unable to significantly increase the yield of pyridine formation by varying solvent (benzene, toluene), radical source (hexamethylditin) variation of reactant ratios, time and temperature. The formation of intractable material suggests isonitrile polymerisation is a competing pathway.

The likely mechanism for pyridine formation involves initial addition of the alkyl radical **3** to the isonitrile carbon followed by 5-*exo* ring closure of the imidoyl radical **4** onto the alkyne to afford vinyl radical **5**, Scheme 1. In theory radical **5** may cyclize to either of two positions on the alkene, Scheme 1, *via* either a 6-*endo* or 5-*exo* ring closure and thence to products **6** or **7**. With each of the examples investigated only one pyridine product was obtained. For isonitrile **1a** (where $R \neq R^1$) with alkyne **2a** the product was identified by X-ray analysis as **6a** † rather than the alternative **7a** thereby suggesting 6-*endo* closure as the preferred route.

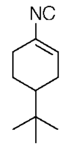
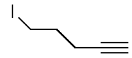
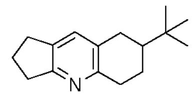
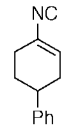
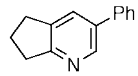
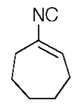
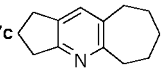
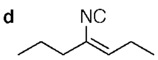
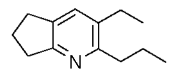
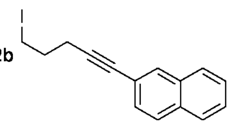
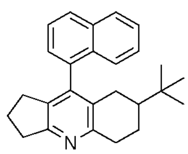
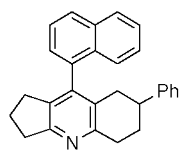
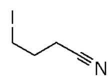
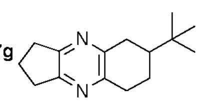
The scope of the methodology was expanded by the use of a substituted iodoalkynes (namely 5-iodo-1-naphthylpent-1-yne (Scheme 1, Table 1)) with vinyl isonitriles **1a** and **1b** which afforded the desired products albeit in moderate yield. In addition we have examined the use of iodonitrile **2c** for the formation of a cyclopenta-fused pyrazine in an analogous manner.[3] Pyrazine **6g** was obtained in 66% yield with isonitrile **1a**.

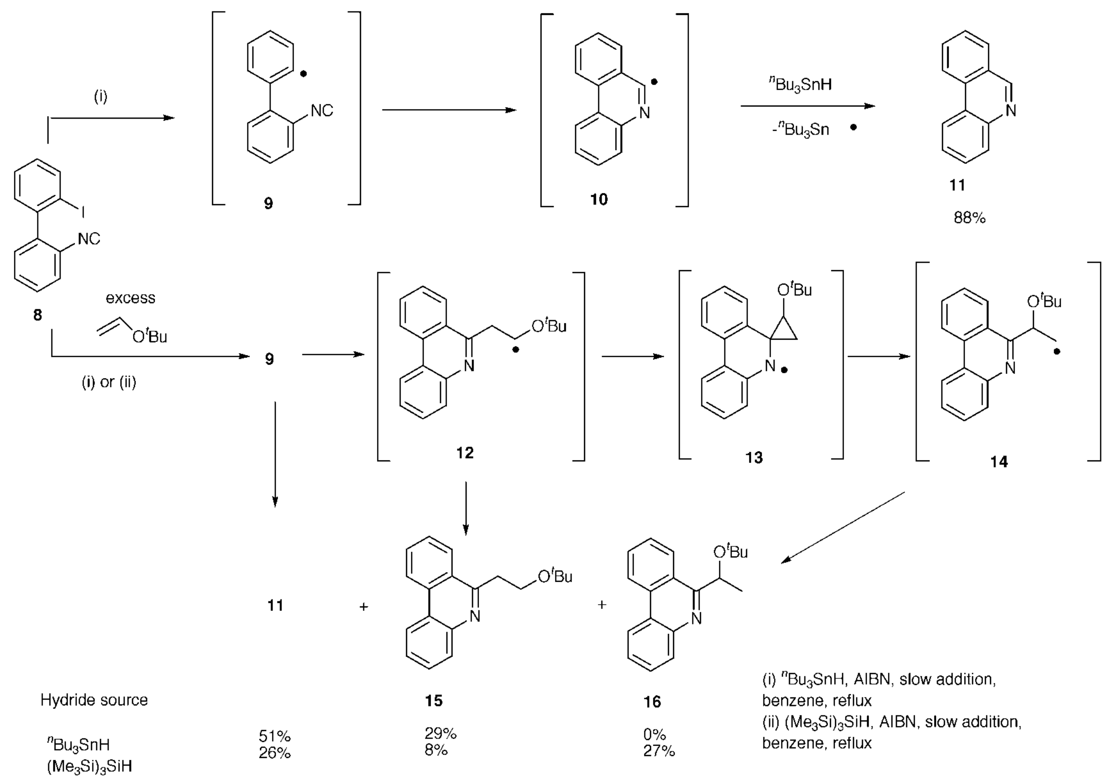


Scheme 1

In an attempt to further the utility of isonitriles in radical cascade processes we are currently investigating intramolecular radical addition to both vinyl and aryl isonitriles. Herein we report the first example of intramolecular radical addition to an aryl isonitrile and the subsequent intermolecular trapping of the so formed imidoyl radical. Thus iodoisonitrile **8** was prepared from 2,2′-dinitrobiphenyl. Treatment of **8** with tri-*n*-butyltin hydride–AIBN resulted in the formation of phenanthridine **11** presumably *via* aryl and imidoyl radicals **9** and **10**. Treatment of **8** with electron rich alkenes such as *tert*-butyl vinyl ether with the slow addition of $^{n}Bu_3SnH$–AIBN resulted in the formation of **15** although phenanthridine **11** remained the major product. Not suprisingly this electron rich alkene reacts more readily with the electron deficient imidoyl radical than do more electron deficient alkenes and alkynes. No trapping was observed with methyl propiolate and hex-1-ene under identical conditions. Interestingly the use of a weaker hydrogen atom donor tris(trimethylsilyl)silane with *tert*-butyl vinyl ether resulted in increased addition of the imidoyl radical to the enol ether although we now obtained a new product **16** which we believe to have resulted from rearrangement *via* **13** and **14**. The driving force for the rearrangement is, however, not

Table 1

Isonitrile	Alkyne or nitrile	Pyridine	Yield (%)
1a 	**2a** 	**6a** 	66%
1b 	**2a**	**6b** 	72%
1c 	**2a**	**6c** = **7c** 	36%
1d 	**2a**	**6d** 	46%
1a	**2b** 	**6e** 	23%
1b	**2b**	**6f** 	20%
1a	**2c** 	**6g** = **7g** 	66%



Scheme 2

immediately obvious (Scheme 2). The intramolecular addition to an aryl or vinyl isonitrile combined with intramolecular trapping of the intermediate imidoyl radical is currently under investigation for the synthesis of biologically active natural products.

Vinyl isonitriles have rarely been utilised in synthetic applications.[8,9] Herein we have demonstrated that vinyl isonitriles are reasonable substrates in 4 + 1 radical annulations with iodoalkynes and iodonitriles for the formation of cyclopenta-fused pyridines and pyrazines respectively. Both of these moieties constitute interesting pharmacophores for pharmaceuticals and agrochemicals. Finally we have shown that the intramolecular radical addition to isonitriles for the formation of 6-membered rings is synthetically viable and our efforts to utilize this methodology for the preparation of biologically active natural products will be reported in due course.

Acknowledgements

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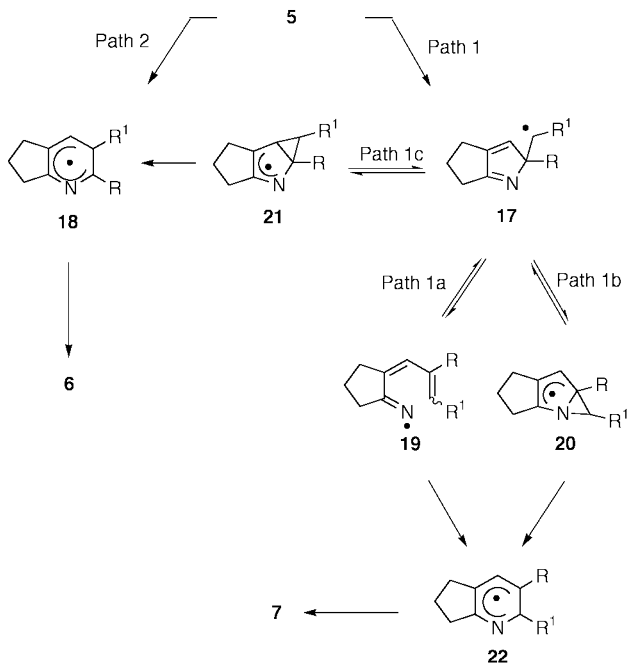
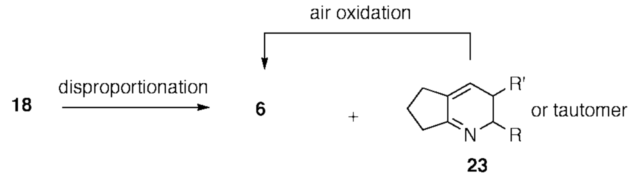
Notes and references

† For **1c** and **1d** ^{1}H and ^{13}C NMR spectra suggested the product was most likely **6c** and **6d** respectively. For **1b** it is not possible to distinguish between the pathways since $R = R^1$. 6-*endo* Ring closure (or alternatively a radical accelerated electrocyclisation reaction) forms six-membered ring product **18** which is then ultimately converted to product **6**, path 2.‡ Pyridine **6** may also arise from 5-*exo* cyclisation of **5** to



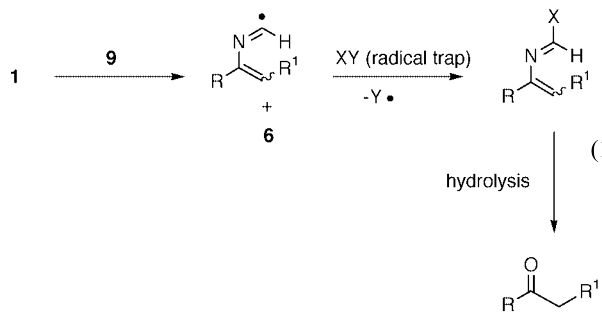
form **17** followed by rearrangement, path 1c. Alternative product **7** may arise from rearrangement of **17** to **22** *via* either **19**, path 1a or **20**, path 1b. With each of the isonitriles **1a–d** investigated only one pyridine product was obtained. The type of ring expansion depicted in paths 1b and 1c is well precedented for simple β-multiply bonded alkyl radicals[2,10] but has rarely been observed for allyl or dienyl radicals.[11] For aryl isonitriles, at least, some experimental evidence exists to suggest that path 1c is not operable[12] and semiempirical calculations[3a] suggest it is likely to be less favourable than a path 2 type process. We therefore believe that path 2 is likely to be the dominant pathway for the conversion of **1** to **6**.

‡ It is necessary to invoke an oxidation step to form **6** from **18**. The formation of aromatised products from dihydroaryl radicals under reductive conditions is not uncommon[13] but as with the aryl isonitriles the oxidant is not immediately obvious. Some evidence exists for the isonitrile itself acting as an oxidising agent.[3a] Should this be the case a



likely by-product with vinyl isonitriles would be the corresponding ketone.§ However, we were unable to detect any ketone from reactions of **1a–d**. Other possibilities include radical disproportionation.[2] Disproportionation of two molecules of **18** would give **6** plus a dihydropyridine moiety **23** which may be air-oxidised to **6** on work-up. On one occasion each with **6c** and **6d** we detected small amounts of a compound whose ^{1}H NMR and mass spectra were consistent with a dihydropyridine moiety. Each compound was subsequently oxidised to the corresponding pyridine on standing in air. It seems likely then that radical disproportionation of **18** plays at least some part in the formation of **6** from **18**.

§ By analogy with the aryl isonitriles described in ref. 3(*a*) should vinyl isonitrile act as oxidising agent it may be expected to lead to formation of a ketone as indicated in eqn. (1).



(1)

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