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Homolytic aromatic substitution: a radical approach towards the synthesis of 5-azaoxindoles

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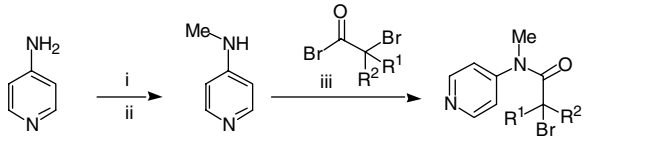
Abstract—A range of 5-azaoxindoles have been synthesised employing homolytic aromatic substitution onto pyridine as the pivotal step.

Inter and intramolecular homolytic aromatic substitution reactions have been used for over a hundred years for the formation of new carbon bonds. Whilst the intermolecular process in general shows a lack of selectivity, there are a few isolated cases where it has been used to good effect.[1] The intramolecular variant however has been far more widely utilised and has seen something of a revival over the past 15 years, with many examples of cyclisation onto arenes as well as onto heteroarenes being reported.[2]

For some time, we have had an interest in the synthetic[3] and mechanistic[4] aspects of homolytic aromatic substitution but have as yet not investigated this approach as a method to synthesise fused pyridine-based systems. It appears that there has been little interest in the synthesis of fused pyridine systems using this method and as far as we are aware there have been only two reports of an alkyl radical undergoing an intramolecular radical cyclisation onto pyridine ring systems. The first of these was described by Murphy[5] and the second more recently by Zard.[6] We viewed azaoxindoles as worthy synthetic targets to test this approach, as they have many potential biological applications, one of which is the suppression of TrK tyrosine kinases,[7] which have been implicated in the development of various cancers including breast and prostate cancers.[8] Moreover, we wished to be able to generate a spirocyclic centre at the 3-position of these systems which would lead ultimately to bioisosteres of simple spirocyclic alkaloids such as horsfiline for biological evaluation.

To our surprise it appears that there are only two methods documented towards the synthesis of 5-azaoxindole systems. One approach was based upon the dilithiation of pivaloylamino pyridine, followed by carbon monoxide insertion.[9] The other approach involved the bromination of 5-azaindole, followed by reduction to give the 5-azaoxindole.[10] Both of these methods suffer from relatively harsh reaction conditions and limited applicability. Herein, we wish to disclose our investigations directed towards the synthesis of a range of 5-azaoxindoles using the cyclisation of an alkyl radical onto a pyridine ring as the key synthetic step.

It was envisaged that preparation of the cyclisation precursors **2a**–**c** (Scheme 1) could be achieved simply by treatment of amino pyridine with the appropriate haloacid halide. Along these lines, 4-aminopyridine in the presence of triethylamine or Hünig's base was treated with 2-bromopropionyl bromide. Unfortunately,



2a. $R^1 = R^2 = H$ 61%
2b. $R^1 = Me$, $R^2 = H$ 75%
2c. $R^1 = R^2 = Me$ 86%

Scheme 1. Reagents and conditions: (i) $ClCO_2Et$, Hünig's base, DCM; (ii) $LiAlH_4$, THF; (iii) Hünig's base, DCM.

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complex mixtures of products were formed and poor yields of the desired amides resulted. The alternative strategy that we chose to adopt involved mono-methylation of the 4-aminopyridine to give **1** followed by acylation with a bromoacid bromide. Two methods for the formation of **1** were investigated. The first, developed by Reese[11] involved the reaction of 4-aminopyridine with formaldehyde and *p*-thiocresol in acetic acid followed by reduction with sodium borohydride which gave **1** in 50% yield. The second approach involved acylation of 4-aminopyridine with ethyl chloroformate followed by reduction with a 1 M solution of $LiAlH_4$ in THF. This method gave the desired amine **1** in 75% yield on a multigram scale. The requisite radical precursors were then generated by treatment with the appropriate bromoacid bromides, and Hünig's base in dichloromethane (Scheme 1). Hence, reaction of **1** with 2-bromopropionyl bromide and 2-bromoisobutyryl bromide gave the corresponding cyclisation precursors **2b** and **2c** in 75% and 86% yields, respectively. Similarly, treatment of **1** with 2-bromoacetyl bromide gave **2a** as judged by NMR analysis of the crude reaction mixture. However, **2a** was never isolated in a pure form due to its rapid decomposition. Indeed all three of the α-bromo amide cyclisation precursors proved to be relatively unstable and required storage in the dark at low temperature.

Compounds **2b** and **2c** were subjected to standard tributyltin hydride (TBTH) mediated radical cyclisation conditions (1.5 equiv of TBTH, 0.1 equiv of AIBN, 1.0 equiv of substrate at a concentration of approximately 0.1 M in toluene at reflux) (Scheme 2). No cyclisation product was detected and surprisingly there was no evidence of the product resulting from direct reduction with TBTH in either of these reactions; indeed, the major product in each case was unreacted starting material along with some decomposition products (entries 1 and 2 in Table 1). When these reactions were repeated using 2 equiv of AIBN, all of the starting material was consumed giving the desired cyclised product and directly reduced product (entries 3 and 4). These results are in accord with the mechanistic proposals that we previously outlined[4] where at least one full equivalent of AIBN was required for successful homolytic aromatic substitution involving both benzene and imidazole ring systems.

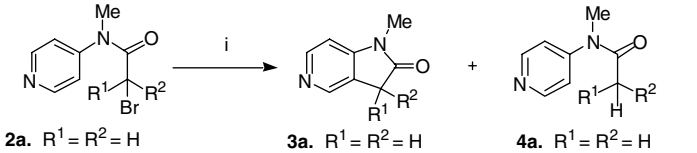
Given the less than ideal yields of cyclisation products from these reactions, effort was directed at improving the synthesis by the slow addition of TBTH and AIBN via syringe pump over a 5 h period. This strategy had little effect on the yield of cyclised product from the cyclisation of **2b** (entry 5) but was effective in significantly increasing the yield of **3c** from **2c** (entry 6). No identifiable cyclisation product, reduced product or starting material could be isolated from the reaction involving **2a**. The combined yield of cyclised and reduced products from cyclisation of the secondary bromide precursor **2b** was considerably less than that from the tertiary bromide precursor **2c**. The stability of the secondary bromide **2b** to silica during chromatography was also less than **2c**, and **2b** appeared to decompose under the cyclisation conditions to some extent. The primary bromide **2a** appeared to be the least stable, indeed, upon heating **2a** alone in deoxygenated toluene for 30 min resulted in complete degradation. The stability of the starting bromide under the reaction conditions, prior to radical formation therefore appears to be largely responsible for the differences in yields observed.

Table 1. Yield of cyclised product and directly reduced product

Entry	Cyclisation precursor	Isolated yield (%)			
		Cyclised product		Directly reduced product	
1[a]	**2b**	**3b**	0	**4b**	0
2[a]	**2c**	**3c**	0	**4c**	0
3[b]	**2c**	**3c**	41	**4c**	40
4[b]	**2b**	**3b**	3	**4b**	25
5[c]	**2b**	**3b**	7	**4b**	24
6[c]	**2c**	**3c**	68	**4c**	17
7[c]	**2a**	**3a**	0	**4a**	0
8[c]	**5a**	**6a**	55	**7a**	21
9[c]	**5b**	**6b**	73	**7b**	11
10[c]	**5c**	**6c**	76	**7c**	12
11[c]	**5d**	**6d**	71	**7d**	10

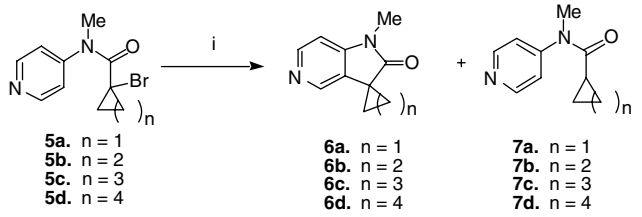
[a] TBTH (1.5 equiv), AIBN (0.1 equiv), substrate (1.0 equiv) as a 0.1 M solution in toluene.
[b] TBTH (1.5 equiv), AIBN (2.0 equiv), substrate (1.0 equiv) as a 0.1 M solution in toluene.
[c] Syringe pump addition over 5 h of TBTH (1.5 equiv) and AIBN (2 equiv) to substrate (1.0 equiv) as a 0.1 M solution in toluene making a 0.05 M solution upon complete addition.

We next directed our attention to the synthesis of spirocyclic 5-azaoxindoles for which we are unaware of any previously reported synthetic methods. The synthesis of the cyclisation precursors was achieved by the reaction of **1** with the appropriate bromoacid bromide. The bromoacid bromides required to synthesise **5b–d** were prepared from commercially available acids using Hell–Volhard–Zelinsky bromination conditions employing 2.5 equiv of bromine and a catalytic amount of red



2a. $R^1 = R^2 = H$ **3a.** $R^1 = R^2 = H$ **4a.** $R^1 = R^2 = H$
2b. $R^1 = Me, R^2 = H$ **3b.** $R^1 = Me, R^2 = H$ **4b.** $R^1 = Me, R^2 = H$
2c. $R^1 = R^2 = Me$ **3c.** $R^1 = R^2 = Me$ **4c.** $R^1 = R^2 = Me$

Scheme 2. Reagents and conditions: (i) Bu_3SnH, AIBN, toluene, 110 °C.



Scheme 3. Reagents and conditions: (i) Bu_3SnH, AIBN, toluene, 110 °C.

phosphorus. Each was purified by fractional distillation prior to coupling with **1** under the conditions previously adumbrated to give the cyclisation precursors **5b–d** in 86%, 85% and 81% yields, respectively. For the preparation of **5a**, 1-bromocyclopropanecarbonyl chloride was synthesised by intramolecular cyclisation of 2,4-bromobutanoate in the presence of tetrabutylammonium hydrogen sulfate and potassium carbonate in toluene, to give the monobromoester. This was then treated with 6 M HCl to furnish the bromoacid, followed by conversion to the acid chloride by treatment with thionyl chloride giving 1-bromocyclopropanecarbonyl chloride in 56% yield.[12] This was then coupled with **1** to give **5a** in 83% yield.

The cyclisation of substrates **5a–d** (Scheme 3) afforded a range of spiro azaoxindoles in reasonable yields (entries 8–11). With the exception of the cyclisation of **5a** it would appear that the size of the spirocyclic ring has little effect on the selectivity between cyclisation and direct reduction with TBTH. Interestingly, the cyclisation of **5a** gave significantly less cyclisation product than the other cases investigated even though the reactivity of a cyclopropyl radical has been shown to be similar to a vinyl radical. This is about one order of magnitude less reactive than a phenyl radical, but considerably more reactive than an alkyl radical in addition reactions to β-methylstyrene, styrene and benzene.[13] These are all of course electron-rich aromatic systems compared to pyridine. Of the four tertiary radicals being considered in this series, the cyclopropyl radical resulting from **5a** is the least nucleophilic[14] and consequently the rate of cyclisation of this radical would be expected to be the slowest of those investigated with the electron-poor pyridine ring system.

As all the reactions were conducted under essentially identical conditions, the ratio of cyclised to reduced products for each substrate provides an approximate value for k_c/k_H, where k_c is the rate constant for the rate-determining step of cyclisation, and k_H is the rate constant for hydrogen atom transfer from the TBTH to the uncylised radical. Knowing the rate of the bimolecular hydrogen atom transfer process, a rate for cyclisation into the pyridine ring can be calculated. This work is ongoing in our laboratories.

In general, we have demonstrated the feasibility of using homolytic aromatic substitution onto pyridine as an efficient route to synthesise 5-azaoxindoles and spirocyclic 5-azaoxindoles. Clearly, the main limitation to this method is the instability of the α-bromoamide cyclisation precursors making this method poor when secondary α-bromoamides are involved, and inappropriate when primary α-bromoamides are involved.

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References and notes

1. Recent examples include: McLoughlin, P. T. F.; Clyne, M. A.; Aldabbagh, F. *Tetrahedron* **2004**, *60*, 8065–8071; Núñez, A.; Sánchez, A.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron* **2004**, *60*, 6217–6224.
2. Recent leading references include: Review: Studer, A.; Bossart, M. In *Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, p 62; Bowman, W. R.; Cloonan, M. O.; Fletcher, A. J.; Stein, T. *Org. Biomol. Chem.* **2005**, *3*, 1460–1467; Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2002**, *41*, 4191–4193; Escolano, C.; Jones, K. *Tetrahedron* **2002**, *58*, 1453–1464; Bowman, W. R.; Mann, E.; Parr, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2991–2999; Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron* **2002**, *58*, 3387–3400; Flannagan, S. R.; Harrowven, D. C.; Bradley, M. *Tetrahedron Lett.* **2003**, *44*, 1795–1798.
3. Beckwith, A. L. J.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1995**, 977–978.
4. Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 95–98.
5. Murphy, J. A.; Sherburn, M. S. *Tetrahedron* **1991**, *47*, 4077–4088.
6. Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2004**, *21*, 3671–3674.
7. Wood, E. R.; Kuyper, L.; Petrov, K. G.; Hunter, R. N.; Harris, P. A.; Lackey, K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 953–957.
8. Tagliabue, E.; Castiglioni, F.; Ghirelli, C.; Modugno, M.; Asnaghi, L.; Somenzi, G.; Melani, C.; Menard, S. *J. Biol. Chem.* **2000**, *275*, 5388–5394.
9. Smith, K.; El-Hiti, G. A.; Pritchard, G. J.; Hamilton, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2299–2303.
10. Mazéas, D.; Guillaumet, G.; Viaud, M. C. *Heterocycles* **1999**, *50*, 1065–1080; Robinson, R. P.; Donahue, K. M. *J. Org. Chem.* **1991**, *56*, 4805–4806.
11. Kemal, O.; Reese, C. B. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1569–1573.
12. Hoffmann, H. M. R.; Eggert, U.; Walenta, A.; Weineck, E.; Schomburg, D.; Wartchow, R.; Allen, F. H. *J. Org. Chem.* **1989**, *54*, 6096–6100.
13. Johnston, L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1984**, *106*, 4877–4881.
14. Walborsky, H. M. *Tetrahedron* **1981**, *37*, 1625–1651.