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LETTERS

Synthesis of heterocyclic compounds using radical reactions

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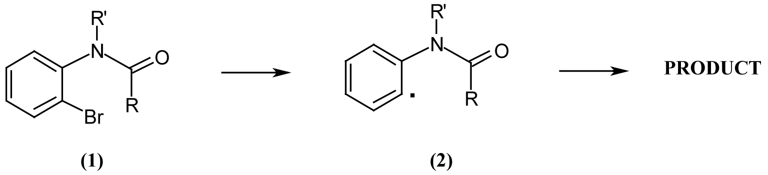
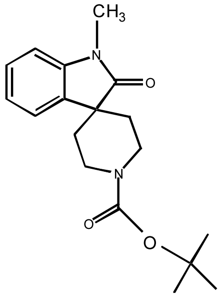
Abstract—A generalised radical reaction has been used to synthesise heterocyclic compounds which could serve as ligands for drug discovery. Attempt also have been made to rationalise the formation of oxidation products formed during TBTH reaction. © 2002 Elsevier Science Ltd. All rights reserved.

We have investigated the following general reaction (Scheme 1) and in this communication we wish to disclose our preliminary results. Compound **1** on treatment with tributyltin hydride (TBTH) generates radical **2**, which then undergoes further reactions and depending upon the substituents R and R^1 gives a number of structurally different ligands which could possibly be used in drug discovery.



Scheme 1.



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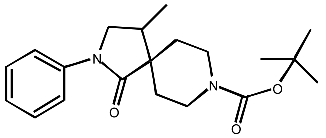

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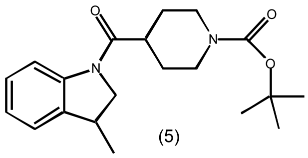

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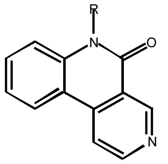

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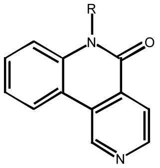

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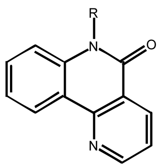

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Keywords: radical reactions; heterocyclic chemistry.

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Several reactions of this kind are known in the literature.[1–5] However in the present work we were interested to synthesise compounds **3**–**8**.

Although the above structures are varied in nature but they could all be derived from **2**. Thus, bromoaniline **9** was converted to **11** and **12**, as shown in Scheme 2. Reaction of **11** in toluene solution with TBTH in the presence of AIBN at 100°C for 2 h yielded compound **3**[6] (25%).[7]

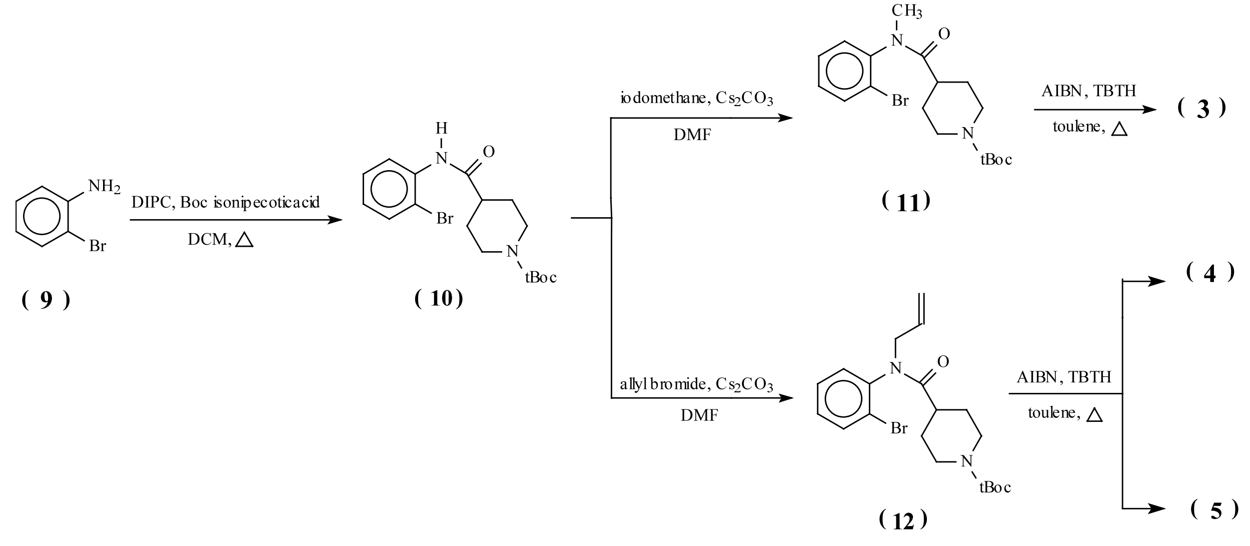
Similarly following the above condition compound **12** gave **4** as the major product (75%) and **5** as the minor component (8%).

Reaction of compound **12** to give **4** and **5** could be rationalised, as shown in Scheme 3. Thus, the initial radical **13** undergoes *exo* cyclisation followed by the capture of the newly formed radical by hydride gives **5**. Compound **4** on the other hand is formed by the rearrangement of **13** to the more stable radical **14** followed by *exo* cyclisation.

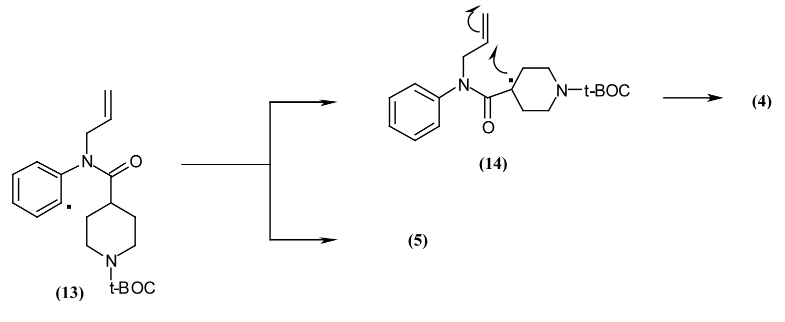
The reaction of **11** to yield **3** is more difficult to rationalise, however, it should be noted that there are several reports in the literature[2] describing the formation of oxidation products during TBTH reactions. One such reaction involves the conversion of **15** to **17** using TBTH reaction. It has been speculated[2] that this type of conversion involves pseudo $S_{RN}1$ mechanism. Thus, the radical **16** undergoes rearrangement to **18** either by direct *endo* cyclisation or through the intermediacy of the *exo* cyclisation product, which rearranges rapidly to the more stable radical **18**. In the presence of TBTH which acts both as a radical generator and a base, the radical **18** is converted to the radical anion **19**. Single electron transfer of **19** yields **17** and **16** and the chain reaction continues (Scheme 4).

This mechanism intrigued us and we argued that if compound **20** is treated with TBTH it should initially yield the radical **21** which could then rearrange in two different pathways to yield the radicals **21a** and **21b**. In the presence of TBTH as a base, these radicals are converted to the radical anions **23** and **22** which then yield **25** and **24**, respectively, following the steps outlined above. The radical **21b** could be obtained as in the case of **16** to **18**, whereas **21a** could arise from the initial radical **26**. It should be mentioned that we have no evidence for the formation of **26** (Scheme 5).

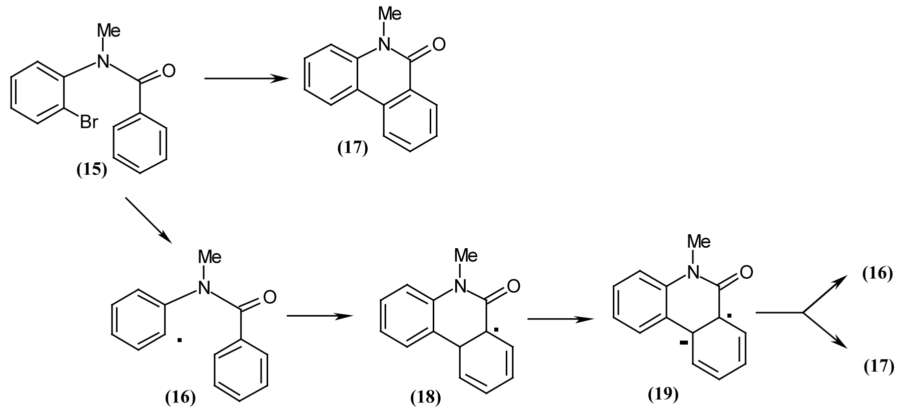
Thus, when **20** was treated with TBTH it indeed yielded **25** (50%) and **24** (23%). We explored further the above radical reactions with compound **27** and obtained **25** (5%), **24** (27%) and **28** (54%). We did not detect the



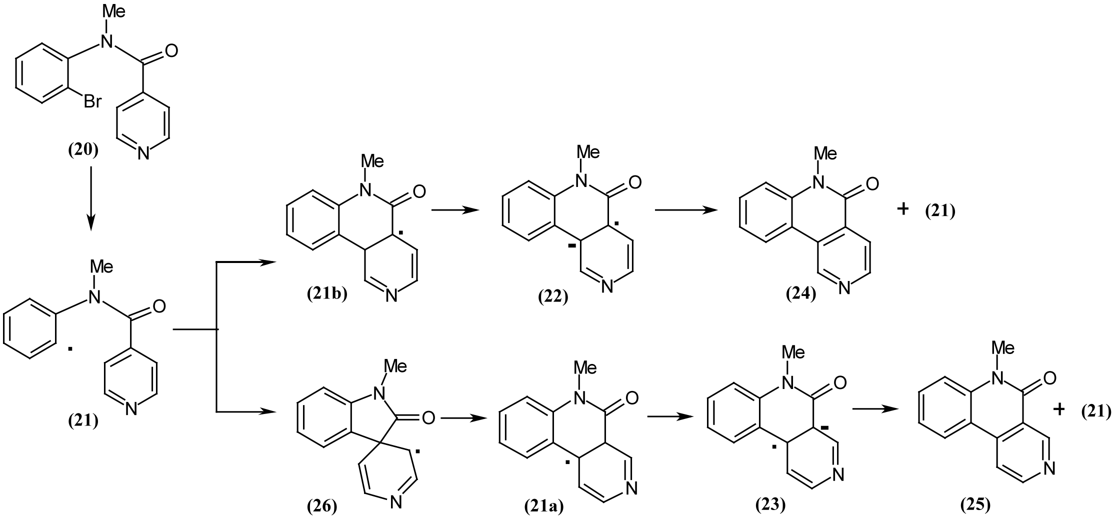
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

formation of **29** in the above reaction. The origin of these products is explained in Scheme 6. Once again the formation of **25** and **28** could be explained as for the conversion of **16** and **17** and the formation of **24** could proceed via the formation of the initial radical **30**.

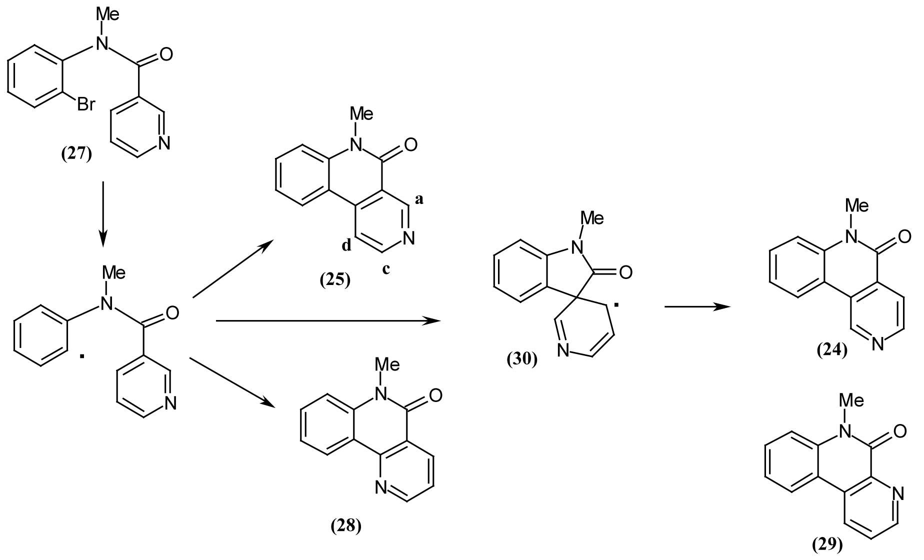
NMR spectra of **25**, **24** and **28** indicate that Ha in these compounds appear at δ 9.7, δ 8.3 and δ 8.8, respectively. Hd in **25** appears at δ 8.1 and δ 9.7 in **24**, whereas Hb appears at δ 8.8 and δ 7.5 in **24** and **28**, respectively. Hc in **25** appears at δ 8.8 and at δ 9.0 for **28**. It should be noted that Ha and Hd are shifted downfield in these compounds from their predicted chemical shift positions in pyridine.

With the hope of quenching the intermediate spiro radical before it underwent further rearrangement, we investigated the radical reaction of **31** and obtained **32** (76%) and there was no evidence for the formation of the rearranged product. Presumably in this case the intermediate spiro radical **33** is more stable and captures hydride radical before undergoing rearrangement (Scheme 7).

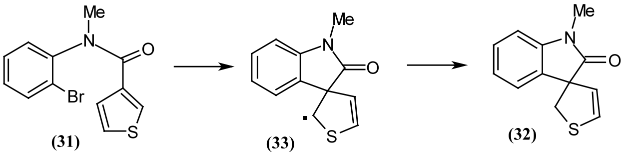
Compound **32** shows the presence of two mutually coupled vinyl hydrogens at δ 5.3 and δ 6.5 and a CH_2 group at δ 3.9 and δ 3.4. In the CNMR spectrum the quarternary spiro carbon appears at 62 ppm and CH_2 appears at 41 ppm.

Acknowledgements

We would like to sincerely thank Schering-Plough Research Institute, Kenilworth, NJ, for financial support.



Scheme 6.



Scheme 7.

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6. NMR and high-resolution mass spectra of all the compounds described in this communication were consistent with the assigned structures. Assignments of structures were further confirmed using HMBC and NOE experiments.
7. The percentages in parenthesis indicate yields. All the compounds described in this paper were crystalline excepting compound **4** which was an oil. The melting points of compounds **3**, **5**, **14**, **25**, **24**, **28** and **32** were 133–135, 124–125, 96–98, 194–196, 197–199, 173–175 and 114–115°C, respectively. Crystals were obtained from dichloromethane and hexane.