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Synthesis of heterocyclic compounds using radical reactions and evidence for the formation of spiro radical intermediates

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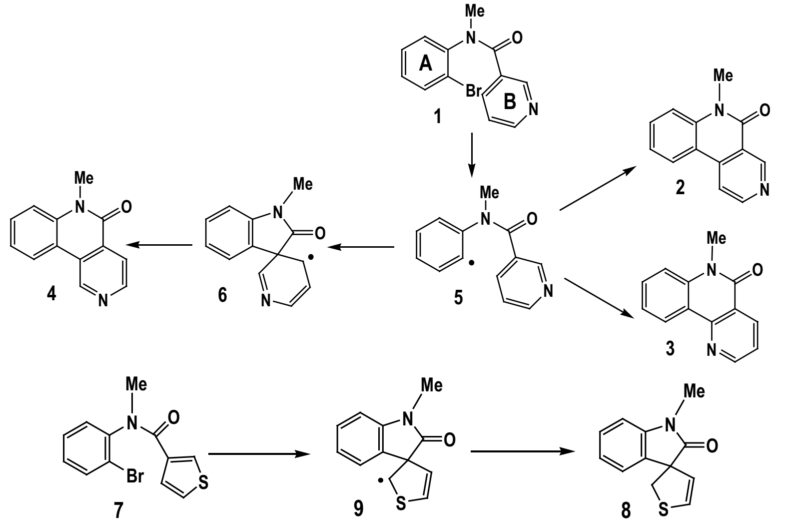
Abstract—Synthesis of novel heterocycles using radical reactions have been described. Reaction mechanism of their formation is also presented.

In a recent publication[1] we have shown, for example, that compound **1** when treated with tributyl tin hydride (TBTH) yields **2**, **3**, and **4**. Presumably they are formed[1–3] through the intermediacy of radicals **5** and **6**. However in our earlier studies we were unable to capture the spiro radical derived products. We then investigated[1] the radical reaction with the thiophene carboxyamide **7** and obtained exclusively compound **8** suggesting that the intermediate spiro radical **9** was more stable than **6**.

Intrigued by this observation we decided to extend our studies with the following general structures **10** wherein x = –CH=CH–, –S–, –O–, or –N–R and in this communication we wish to report our results. It should be



Keywords: Radical reactions; Heterocyclic chemistry.

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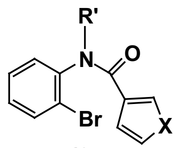
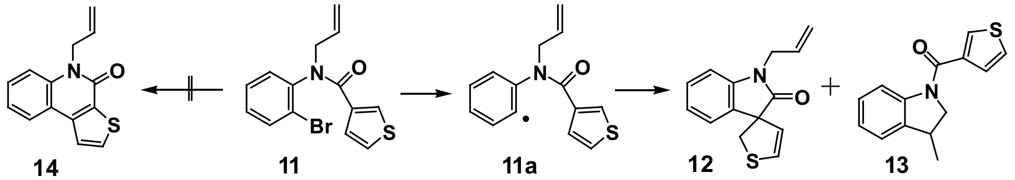
noted that although the yields have not been optimized the reactions described in this communication yield a variety of heterocycles some of which could serve as pharmacophores for making libraries of compounds for biological testing.



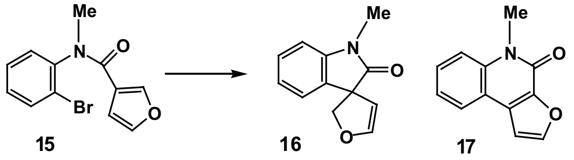
10

Reaction of the thiophene carboxyamide **11**[4] with TBTH yielded the spiro indole **12** (62%) and compound **13** (20%) indicating that given a chance the radical such as **11a** will add to the thiophene double bond or the allyl substituent without undergoing rearrangement to the fused aromatic compound **14**.

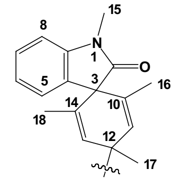
We investigated the substitution effect on the phenyl ring that is the ring B of the benzamide residue to detect the formation of spiro radical derived products. Specifically we were interested in the results with benzamides such as 2:6-dimethyl and 2:4:6-trimethyl substituted benzamides **24** and **25**, respectively. When **24** was treated with TBTH it yielded **26** (62.5%) and a pair of *anti* dimers **27** (6.2%) and **28** (10.8%) and a *syn* dimer **29** (7.5%). The reaction of **25** with TBTH yielded **30** (52.3%), **31** (17.6%), and again a pair of *anti* dimers **32** (3.9%) and **33** (4.5%) and a *syn* dimer **34** (4.5%) were obtained. These dimers were presumably formed via spiro radical such as **35** (differently substituted by methyl groups) and **31** was formed by rearrangement of **35** to **35a** followed by the loss of a methyl radical. It should be noted that we did not observe this rearrangement in every case studied.



In the case of furan-3-carboxyamide **15** the reaction with TBTH yielded the spiro compound **16** (59%) and no rearrangement product **17** was detected. These results are in contrast with the one seen with compound **10** in which x is –CH=CH– wherein no spiro oxindole was formed.[1]

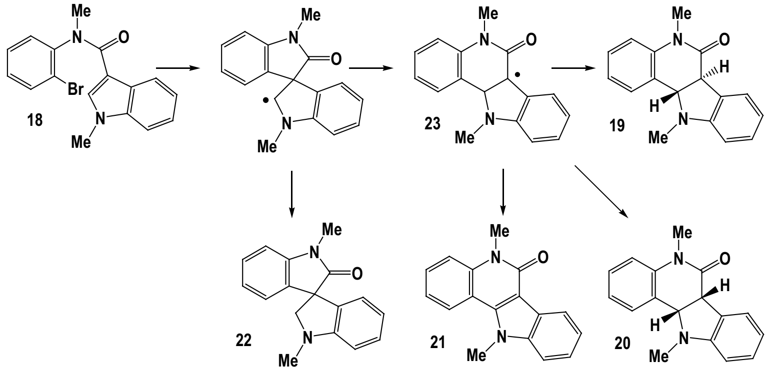


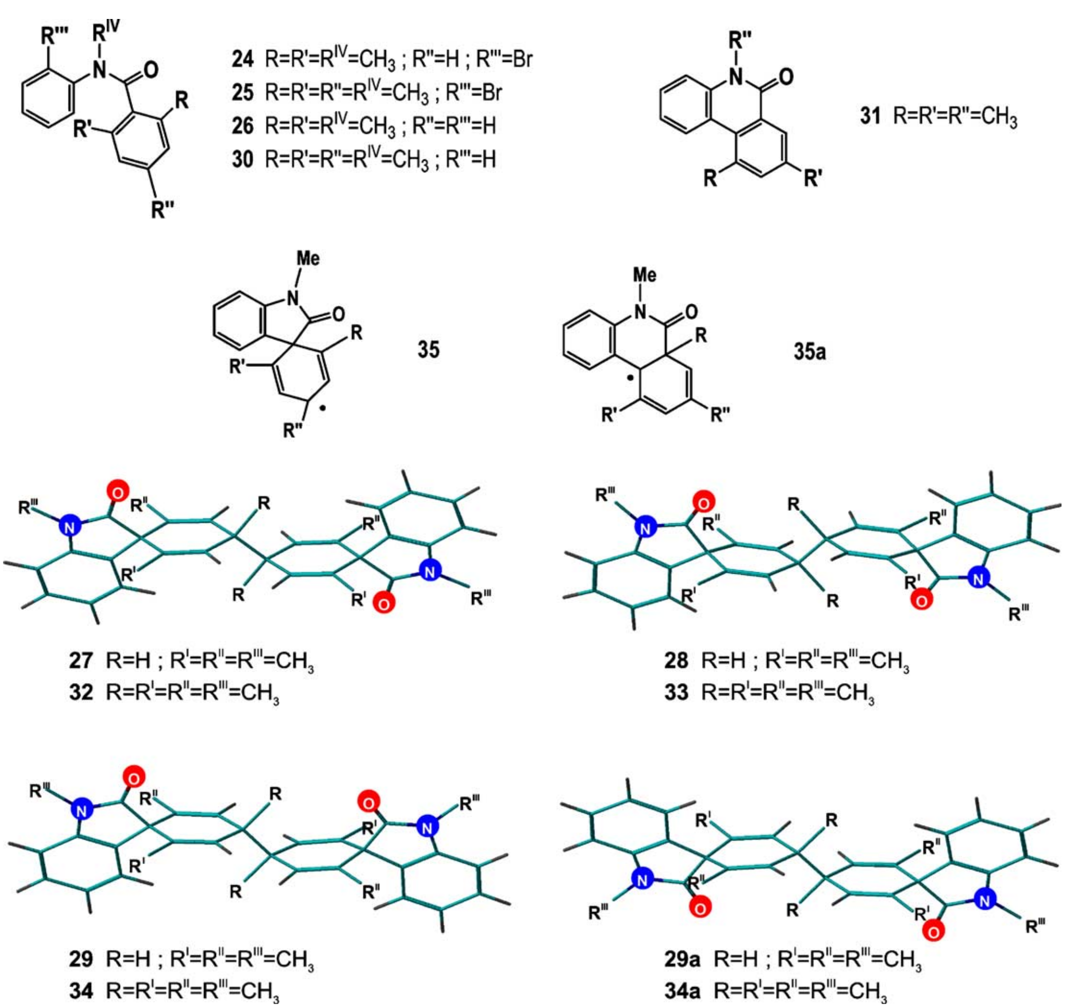
We then investigated the TBTH reaction with compound **18** and obtained **19** (20%), **20** (16%), **21** (47.2%), and **22** (8%). As is evident in this case the spiro radical intermediate derived compound **22** was obtained as a minor component and the main products were derived by rearrangement of the spiro radical to the radical **23**, which either accepts hydrogen radical to give *cis* **20** and *trans* **19** and in addition the radical **23** also undergoes oxidation to yield compound **21**.



The structures of the above dimers were assigned based on extensive NMR studies,[5] details of which will be published elsewhere. A brief summary is presented here.

Energy minimization calculations of **32**, **33**, and **34** were performed using software PCModel (Serena Software, version 7) and MMX force field. In the minimum energy conformations the two methyl groups (3H-17) are in *anti* positions. These dimers give rise to four possible structures as shown in Figure 1. In structures **32** and **33** the oxindole ring carbonyl groups are *anti* to each other and they are *syn* to each other in **34** and **34a**. The structures **34** and **34a** are, however, identical and therefore there are three distinct dimeric structures possible. Similarly **29** and **29a** are identical.





24 $R=R'=R^{IV}=CH_3$; $R''=H$; $R'''=Br$
25 $R=R'=R''=R^{IV}=CH_3$; $R'''=Br$
26 $R=R'=R^{IV}=CH_3$; $R''=R'''=H$
30 $R=R'=R''=R^{IV}=CH_3$; $R'''=H$

31 $R=R'=R''=CH_3$

35

35a

27 $R=H$; $R'=R''=R'''=CH_3$
32 $R=R'=R''=R'''=CH_3$

28 $R=H$; $R'=R''=R'''=CH_3$
33 $R=R'=R''=R'''=CH_3$

29 $R=H$; $R'=R''=R'''=CH_3$
34 $R=R'=R''=R'''=CH_3$

29a $R=H$; $R'=R''=R'''=CH_3$
34a $R=R'=R''=R'''=CH_3$

Figure 1.

All three structures **32**, **33**, and **34** have a plane of symmetry containing the *C*-methyl and *N*-methyl groups. For each *anti* isomers there is also a center of symmetry therefore the NMR (proton and carbon) spectra of **32** and **33** are very simple. Besides the aromatic hydrogens the NMR spectra of **32** and **33** show (the figures in parentheses represent **33**) singlets at 1.30 (1.27) ppm (3H-17), 1.35 (1.33) ppm (3H-16 and 3H-18), 3.27 (3.26) ppm (3H-15) and 5.81 (5.77) ppm (H-11 and H-13). The two *anti* isomers can be distinguished from each other by the size of the NOE observed between H-5 and 3H-17. The distance between these hydrogens is 2.5 Å in **32** compared to 3.5 Å in **33** and hence larger NOE was observed with **32**.

In the case of *syn* isomer **34** there is a plane of symmetry but the two halves of the molecule are not equivalent and therefore the NMR spectra are more complicated that is there are twice the number of signals in **34** compared to **32** and **33**.

The above arguments for assigning the structures of the dimers are also valid for the dimers **27**, **28**, and **29**. For example in the *anti* dimers **27** and **28** besides the aromatic protons there are four singlets (the figures in parentheses refers to **28**) at 1.34 (1.38) ppm (3H-16 and 3H-18), 3.11 (3.33) ppm (H-17), 3.24 (3.28) ppm (3H-15), and 5.84 (5.80) ppm (H-11and H-13). NOE experiments confirmed the assignment of the structures of **27** and **28**. *syn* Dimer **29** again showed double the number of peaks compared to the *anti* dimers.

Acknowledgements

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References and notes

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4. NMR and high resolution mass spectra of all the compounds described in this paper were consistent with the assigned structures. Assignments were further confirmed using HMBC and NOESY experiments.
5. Excepting compound **30**, which was oil, and compounds **22**, **27**, **28**, **29**, **32**, **33**, and **34**, which were white solids, all the other compounds described in this paper were crystalline. Crystals were obtained from dichloromethane and hexane. The melting points of compounds **11**, **12**, **13**, **15**, **16**, **18**, **19**, **20**, **21**, **24**, **25**, **26**, and **31** were 89–91, 65–67, 75–77, 67–69, 79–80, 142–143, 127–128, 148–149, 177–178, 105–107, 64–66, 51–52, and 138–140 °C, respectively. Yields are indicated in parentheses.