Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 45 (2004) 8909–8912

Tetrahedron Letters

Synthesis of highly condensed heterocycles using radical reactions

A. K. Ganguly,[a,*] C. H. Wang,[a] J. Misiaszek,[a] T. M. Chan,[b]
B. N. Pramanik[b] and A. T. McPhail[c]

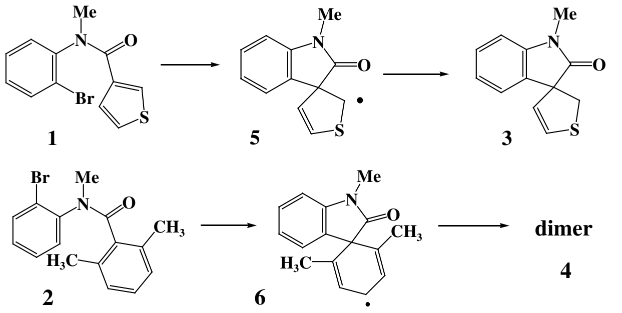
[a]*Stevens Institute of Technology, Hoboken, NJ 07030, USA*
[b]*Schering-Plough Research Institute, Kenilworth, NJ 07033-1300, USA*
[c]*P.M. Gross Chemical Laboratory, Duke University, Box 90346, Durham, NC 27708-0346, USA*

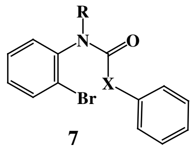
Received 14 September 2004; accepted 27 September 2004
Available online 14 October 2004

Abstract—Using radical chemistry novel highly condensed heterocycles have been synthesized. The mechanism for their formation is discussed.

1. Introduction

In our search for novel heterocycles, which could serve as pharmacophores in drug discovery, we have been exploring radical chemistry[1] to assemble these molecules. Recently we have demonstrated[2] that when compounds such as **1** and **2** are treated with tributyl tin hydride (TBTH) they yield **3** and **4**, respectively. In a separate paper[3] we have discussed the details of the assignments of stereochemistries of the *syn* and *anti* isomers of compound **4**. It should be noted that both **3** and **4** arise through the spiro radicals **5** and **6**, respectively.





7
X= O or N—R

2. Present work

In this communication we would like to report the results of the radical reactions of compounds[4] of general structure **7** wherein X is a heteroatom that is oxygen or substituted nitrogen atoms. As will be evident these reactions have provided us with a novel route for the synthesis of highly condensed heterocycles such as **25** and **38**.

Thus reaction of **8** with TBTH gave mainly the dehalogenated product[5] **9** and a small amount of **10**, which presumably is formed via **11** with the loss of carbon dioxide (Scheme 1). A similar reaction was observed[6] in the case of phenyl sulfonamides wherein the biphenyls were formed with the loss of sulfur dioxide.

We then investigated the radical reaction of compound **12** and obtained **13** (11.0%) and **14** (16.9%) along with the starting material (45%).

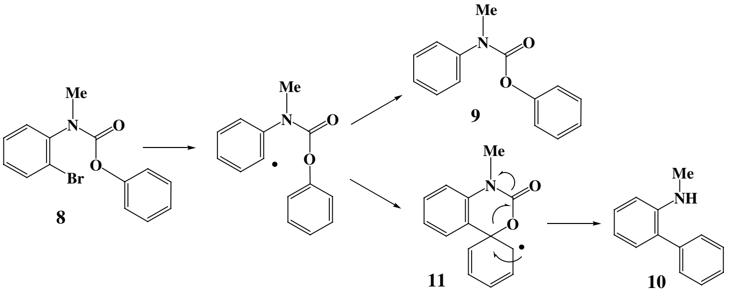
The formation of **13** and **14** can be rationalized, as shown in Scheme 2. Thus, the initial radical **15** undergoes spiro cyclization to give the intermediate **16**, which undergoes further rearrangement, bond cleavage and subsequent

---

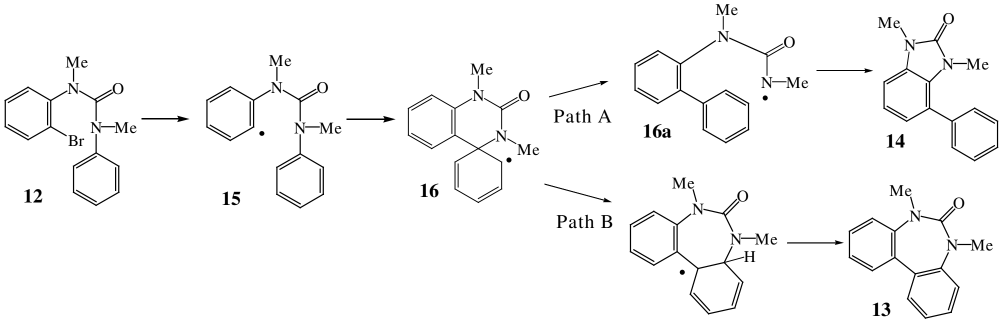
Keywords: Radical reactions; Heterocyclic chemistry.

* Corresponding author. Tel.: +1 201 216 5540; fax: +1 201 216 8240; e-mail: akganguly1@aol.com

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.09.181



Scheme 1.

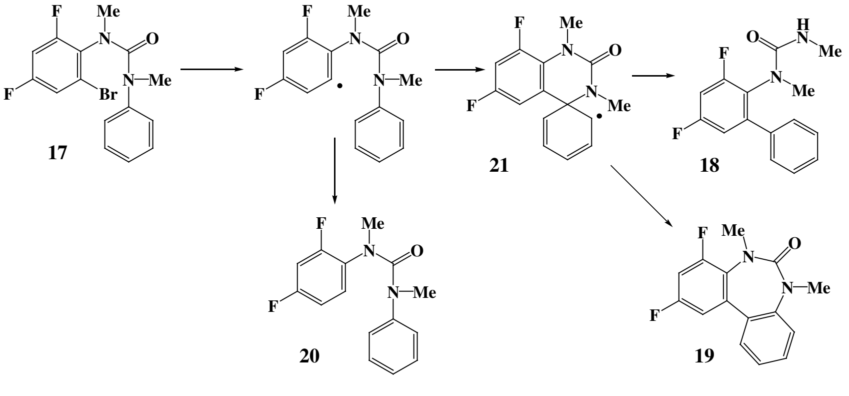


Scheme 2.

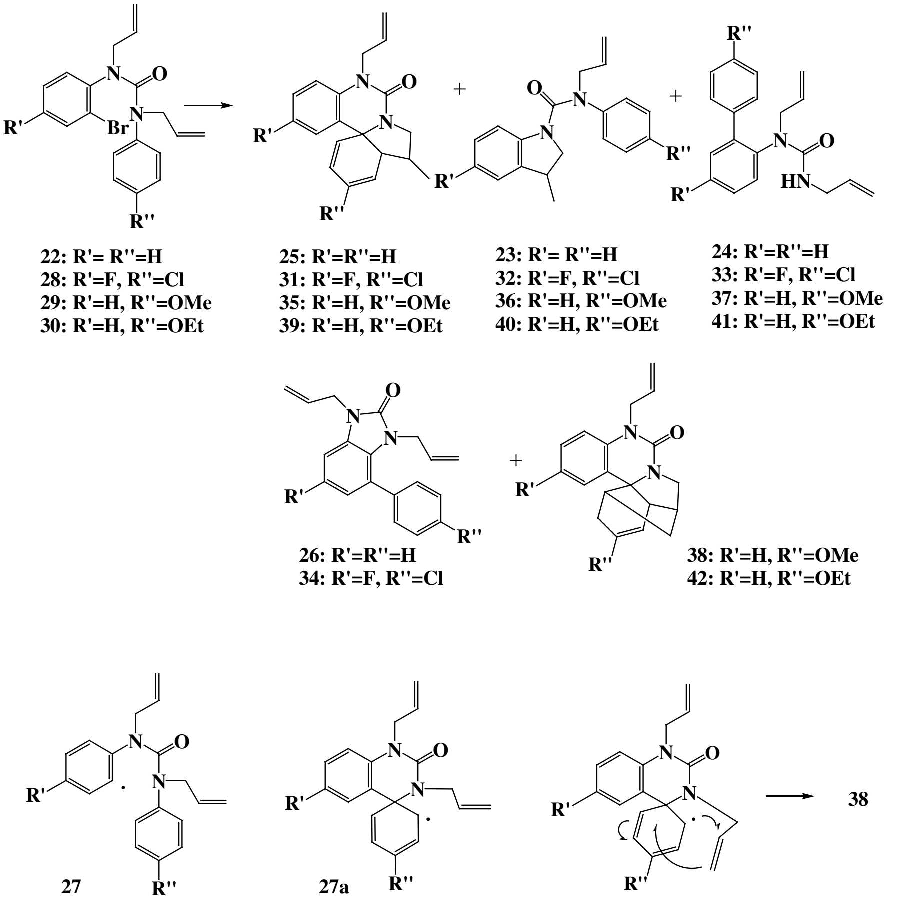
oxidative cyclization (path A) to yield benzimidazole **14** via **16a**, alternatively (path B) the intermediate **16** undergoes bond migration followed by the loss of hydrogen radical to yield **13**. To study the effect in the above radical reaction of an *ortho* substituent to the bromoaniline nitrogen we treated **17** in the usual way with TBTH and obtained **18** (21.6%) and **19** (10.8%) along with the dehalogenated compound **20** (32.4%). The formation of **18** and **19** proceed through the spiro radical **21** as shown in Scheme 3. As suspected in this case we did not detect the formation of the corresponding benzimidazole.

As we intended in the present study to prepare highly condensed heterocycles we explored the possibility of capturing the radical intermediate **16** in an intramolecular sense. Thus when the diallyl derivative **22** was treated with TBTH we obtained **23** (34%) by the cyclization of radical **27** to the allyl group, along with **24** (7%), **25** (13%) and **26** (4.0%). Compounds **24**, **25** and **26** are formed through the intermediacy of the spiro radical **27a**. The structure of **25** was confirmed using X-ray crystallographic studies[7] (see Scheme 5).

We then studied the substitution effects in the above reaction by changing R″ to Cl **28**, OCH_3 **29** and OCH_2CH_3 **30**. Interestingly radical reaction with **28** gave **31** (18.4%), **32** (39.8%), **33** (7.2%) and **34** (3.4%) whereas **29** gave **35** (6.7%), **36** (36%), **37** (5.6%) and **38** (7.2%). Similarly **30** gave **39** (24.8%), **40** (39.6%), **41** (14.2%) and **42** (5.8%). The formation of **38** and **42** follows a cascade reaction as shown in Scheme 4.



Scheme 3.



22: R'= R''=H
28: R'=F, R''=Cl
29: R'=H, R''=OMe
30: R'=H, R''=OEt

25: R'=R''=H
31: R'=F, R''=Cl
35: R'=H, R''=OMe
39: R'=H, R''=OEt

23: R'= R''=H
32: R'=F, R''=Cl
36: R'=H, R''=OMe
40: R'=H, R''=OEt

24: R'=R''=H
33: R'=F, R''=Cl
37: R'=H, R''=OMe
41: R'=H, R''=OEt

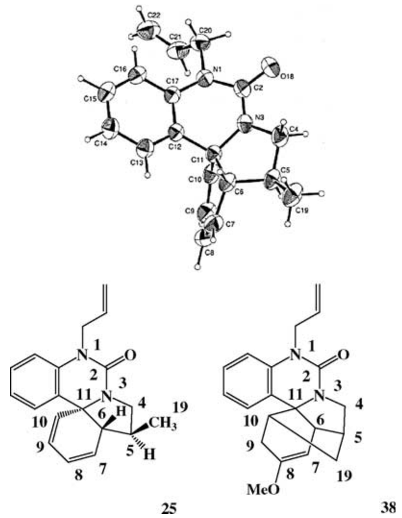
26: R'=R''=H
34: R'=F, R''=Cl

38: R'=H, R''=OMe
42: R'=H, R''=OEt

27

27a

Scheme 4.



25

38

Scheme 5.

The numbering system used in this communication is shown in Scheme 5. In the ^{1}H NMR spectrum of **25** the methyl group appears at δ 1.23 (d), which is absent in **38**. Compound **38** shows H-19 at δ 1.75 (m) and C-19 at δ 34.66. H-9 and H-10 in structure **25** appear at δ 5.9 and 5.7, respectively, which are absent in **38**. In the ^{13}C NMR spectrum of **25** C-9 and C-10 appear at δ 113.75 and 128.85, respectively, which shift in **38** to δ 35.7 and 40.36, respectively. In compounds **25** and **38** C-11 appear at δ 63.46 and δ 63.86, respectively.

3. Conclusion

Using radical reaction we have synthesized several highly condensed heterocycles. Although the yields reported in this communication are not optimized, sufficient amounts of the products described have been made and these will be undergoing biological testing.

Acknowledgements

We wish to sincerely thank Schering-Plough Research Institute, Kenilworth, NJ for generous financial assistance.

References and notes

1. Ganguly, A. K.; Wang, C. H.; David, M.; Bartner, P.; Chan, T. M. *Tetrahedron Lett.* **2002**, *43*, 6865, and references cited therein.
2. Ganguly, A. K.; Wang, C. H.; Chan, T. M.; Ing, Y. H.; Buevich, A. V. *Tetrahedron Lett.* **2004**, *45*, 883.

3. Ganguly, A. K.; Buevich, A. V.; Chan, T. M.; Wang, C. H.; McPhail, A. T. *J. Magn. Reson. Chem.*, submitted for publication.
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, HSQC and COSY experiments.
5. Excepting compounds **23**, **24**, **26**, **28**, **29**, **30**, **32**, **33**, **34**, **35**, **36**, **37**, **41** and **42**, which were oil, all the other compounds described in this paper were crystalline. Crystals were obtained from dichloromethane and hexane. The melting points of compounds **13**, **14**, **18**, **19**, **20**, **25**, **31**, **38**, **39** and **40** were 132–134, 104–106, 120–122, 160–162, 109–111, 80–82, 121–123, 105–107, 60–61 and 72–74 °C, respectively. Yields are indicated in parentheses.
6. da Mata, M. L. E. N.; Motherwell, W. B.; Ujjainwalla, F. *Tetrahedron Lett.* **1997**, *38*, 137.
7. Crystallographic data (excluding structure factors) for compound **25** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 250067. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EX, UK [e-mail: deposit@ccdc.cam.ac.uk].