ORGANIC LETTERS

2010
Vol. 12, No. 4
812−815

Synthesis of Benzoxazolones from Nitroarenes or Aryl Halides

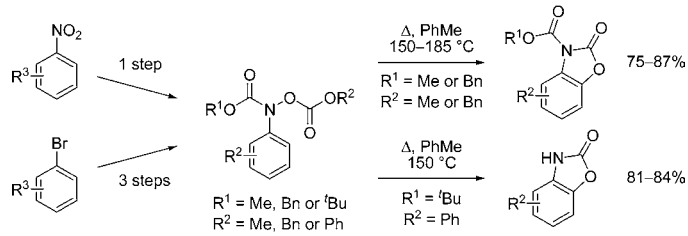
Achim Porzelle,[†] Michael D. Woodrow,[‡] and Nicholas C. O. Tomkinson*[,†]

School of Chemistry, Main Building, Cardiff University, Park Place, Cardiff, CF10 3AT, U.K., and ImmunoInflammation Centre of Excellence for Drug Discovery, GlaxoSmithKline Medicines Research Centre, Stevenage, Hertfordshire, SG1 2NY, U.K.

tomkinsonnc@cardiff.ac.uk

Received December 15, 2009

ABSTRACT



A simple and effective method for the preparation of benzoxazolones from nitroarenes or aryl halides is described. Partial reduction of a nitro group in the presence of a chloroformate followed by a microwave-assisted rearrangement/ring closure sequence provides a convenient and practical procedure to prepare this important pharmacophore. Rearrangement precursors were also accessed from aryl halides through transition-metal-catalyzed coupling.

The benzoxazolone nucleus represents an important pharmacophore present in both pharmaceutical and agrochemical products.[1] Due to the ability of the benzoxazolone core to act as a metabolically stable mimic of phenol, catechol, coumarin, and phenylurethane groups, compounds possessing this structure have a broad spectrum of biological activities. For example, the analgesic Paraflex (**1**),[2] the insecticide and acaricide Phosalone (**2**),[3] and the OP2 agonist **3**[4] all possess a benzoxazolone scaffold (Figure 1).

Methods for the preparation of benzoxazolones generally involve reaction of a 2-aminophenol (e.g., **5**) with a phosgene equivalent. Methods for this transformation are well developed.[5] Therefore, the challenge in their preparation resides in the synthesis of the 2-aminophenol. Synthetic routes to 2-aminophenols are often plagued by multistep, nonselective transformations, and the scaffold is generally purchased

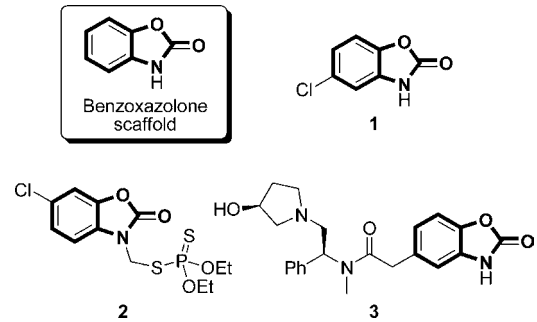


Figure 1. Drug molecules containing a benzoxazolone.

[†] Cardiff University.
[‡] GlaxoSmithKline, Stevenage.

(1) Poupaert, J.; Carato, P.; Colacino, E.; Yous, S. *Curr. Med. Chem.* **2005**, *12*, 877.
(2) Conney, A. H.; Burns, J. J. *J. Pharmacol. Exp. Ther.* **1960**, *128*, 340.
(3) (a) Venugopal, V.; Naidu, V. G.; Prasad, P. R. *Pestology* **2003**, *27*, 29. (b) Ahmad, R.; Kookana, R. S.; Alston, A. M.; Skjemstad, J. O. *Environ. Sci. Technol.* **2001**, *35*, 878. (c) Sanusi, A.; Millet, M.; Mirabel, P.; Wortham, H. *Sci. Total Environ.* **2000**, *263*, 263.
(4) Barber, A.; Bender, H. M.; Gottschlich, R.; Greiner, H. E.; Harting, J.; Mauler, F.; Seyfried, C. A. *Methods Find. Exp. Clin. Pharmacol.* **1999**, *21*, 105.

10.1021/ol902885j
Published on Web 01/21/2010

rather than constructed.[6] This significantly restricts the diversity accessible when introducing this group in medicinal chemistry.

A convenient and controlled strategy to access the 2-aminophenol architecture is by [3,3]-sigmatropic rearrangement of *O*-acyl-*N*-aryl hydroxylamines **6** (R^2 = aryl).[7] If the O-substituent on this rearrangement precursor included a leaving group (e.g., R^2 = OMe), it could be possible to access benzoxazolones directly by intramolecular cyclization after rearrangement. Although the rearrangement of *N*-aryl-*O*-acyl hydroxylamines has been well studied,[7] only a single example of the rearrangement of an *O*-carbonate has been described.[8] This showed that rearrangement of **7** in refluxing xylene gave the protected 2-aminophenol **8** (65%) (Figure 2) where it was suggested this class of substrate should be

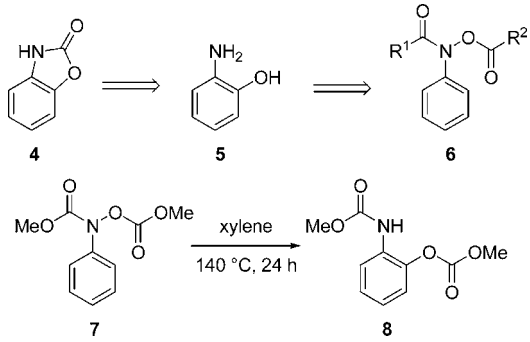


Figure 2. Synthetic strategy for accessing benzoxazolones.

avoided due to sluggish reactivity and reduced yields. Due to the potential of the product from this rearrangement (**7**→**8**) in heterocycle synthesis, we sought to investigate this transformation further. Within this paper we describe a simple synthetic method to access benzoxazolones from nitroarenes or aryl halides through a rearrangement/cyclization strategy.

(5) These methods include the use of dimethyl carbonate: Fu, Y.; Baba, T.; Ono, Y. *J. Catal.* **2001**, *197*, 91. Carbonyl diimidazole: Nachman, R. J. *J. Heterocycl. Chem.* **1982**, *19*, 1545. Urea: (a) Li, F.; Xia, C. *Tetrahedron Lett.* **2007**, *48*, 4845. (b) Bhanage, B. M.; Fujita, S.-I.; Ikushima, Y.; Arai, M. *Green Chem.* **2004**, *6*, 78. (c) Kim, Y. J.; Varma, R. S. *Tetrahedron Lett.* **2004**, *45*, 7205. Carbon Monoxide: (aa) Li, F.; Xia, C. *J. Catal.* **2004**, *227*, 542. (bb) Gabriele, B.; Mancuso, R.; Salerno, G.; Costa, M. *J. Org. Chem.* **2003**, *68*, 601. Chloroformadinium salts: El-Faham, A.; Chebbo, M.; Abdul-Ghani, M.; Younes, G. *J. Herocycl. Chem.* **2006**, *43*, 599.

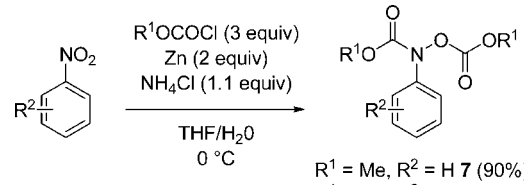
(6) For selected examples of the synthesis of 2-aminophenols and their derivatives see: (a) Koley, D.; Colón, O. C.; Savinov, S. N. *Org. Lett.* **2009**, *11*, 4172. (b) Palmisano, G.; Addamo, M.; Augugliaro, V.; Caronna, T.; García-López, E.; Loddo, V.; Palmisano, L. *Chem. Commun.* **2006**, 1012. (c) Selvam, J. J. P.; Rajesh, S. K.; Reddy, S. R.; Venkateswarlu, Y. *Tetrahedron Lett.* **2006**, *47*, 2507. (d) Khenkin, A. M.; Weiner, L.; Neumann, R. *J. Am. Chem. Soc.* **2005**, *127*, 9988. (e) Sun, H.-B.; Hua, R.; Yin, Y. *J. Org. Chem.* **2005**, *70*, 9071. (f) Kikugawa, Y.; Tsuji, C.; Miyazawa, E.; Sakamoto, T. *Tetrahedron Lett.* **2001**, *42*, 2337, and references therein.

(7) For selected examples on this class of rearrangement, see: (a) Horner, L.; Steppan, H. *Liebigs Ann. Chem.* **1957**, *606*, 24. (b) Oae, S.; Sakurai, T.; Kimura, H.; Kozuka, S. *Chem. Lett.* **1974**, 671. (c) Oae, S.; Sakurai, T. *Tetrahedron* **1976**, *32*, 2289. (d) Gutschke, D.; Heesing, A.; Heuschkel, U. *Tetrahedron Lett.* **1979**, *20*, 1363. (e) Bassoli, A.; Di Gregorio, G.; Galliani, G.; Riboldi, M.; Rindone, B.; Tollari, S.; Chioccara, F. *Bull. Chem. Soc. Fr.* **1988**, 293.

(8) Porzelle, A.; Woodrow, M. D.; Tomkinson, N. C. O. *Eur. J. Org. Chem.* **2008**, 5135.

Preparation of the rearrangement substrates used in reaction development involved partial reduction of nitroarenes in the presence of chloroformates, trapping out the intermediate hydroxylamine (Scheme 1).[9] The reactions were

Scheme 1. Preparation of Protected *N*-Aryl Hydroxylamines

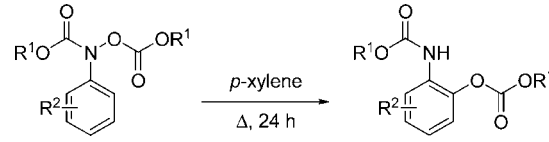


R^1 = Me, R^2 = H **7** (90%)
R^1 = Me, R^2 = 4-Me **9** (92%)
R^1 = Me, R^2 = 3-Me **10** (81%)
R^1 = Me, R^2 = 4-Br **11** (83%)
R^1 = Me, R^2 = 4-I **12** (71%)
R^1 = Bn, R^2 = 4-Me **13** (72%)
R^1 = Me, R^2 = 3-CF_3 **14** (68%)
R^1 = Me, R^2 = 4-CCH **15** (76%)
R^1 = Me, R^2 = 4-Cl **16** (94%)
R^1 = Me, R^2 = 3-Ph **17** (77%)
R^1 = Me, R^2 = 3-Br **18** (71%)
R^1 = Bn, R^2 = H **19** (81%)

generally efficient (68−94% yield) allowing access to a range of stable rearrangement precursors **7** and **9**−**19** that were used throughout this study.

In the development of the thermal rearrangement of these hydroxylamines (**9**−**19**), we modified the conditions previously reported for the rearrangement of **7** (Table 1).[8]

Table 1. Thermal Rearrangement of *N*-Aryl Hydroxylamines[a]



entry	substrate	R^1	R^2	product	% yield[b]
1	**9**	Me	4-Me	**20**	88
2	**10**	Me	3-Me	**21**	75[c]
3	**11**	Me	4-Br	**22**	76
4	**12**	Me	4-I	**23**	72
5	**13**	Bn	4-Me	**24**	83

[a] All reactions conducted on a 1 mmol scale in 5 mL of *p*-xylene. [b] Isolated yield. [c] Product isolated as a 1:1 mixture of regioisomers.

p-Xylene emerged as the optimal solvent, performing the reactions at higher concentration providing consistently higher yields than that previously reported. Reactions were amenable to scale-up and allowed convenient access to a series of protected 2-aminophenols **20**−**24** (entries 1−5; 72−88%).

(9) Porzelle, A.; Woodrow, M. D.; Tomkinson, N. C. O. *Synlett* **2009**, 798.

To improve the transformation further, we examined the effect of microwave heating on rearrangement (Table 2). Heating at high temperatures (>170 °C) resulted in partial decomposition of the protected *N*-aryl hydroxylamine substrate (e.g., **9**) prior to rearrangement. However, reducing the temperature to 150 °C smoothly brought about rearrangement of **9** (entry 1; 88%). Application of this protocol to a series of precursors consistently gave the products in equal or higher yield than conductive heating (entries 1−5; 72−90%). Benzyl carbonates required slightly higher temperatures (160 °C) for the reaction to reach completion inside 3 h (entry 5, 90%; entry 11, 94%). This method offers distinct advantages over conductive heating including: the use of toluene as solvent provides practical advantages over *p*-xylene in isolation and purification; in addition, the reactions were significantly quicker under microwave irradiation (3 vs 24 h). A limitation came from the attempted rearrangement of electron-deficient substrates. Heating a toluene solution of precursor **14** at 150 °C (up to 8 h) led to recovery of starting material (>80%). Attempts to induce rearrangement by heating at higher temperatures (up to 185 °C) were equally unsuccessful (entry 6). At these elevated temperatures, cleavage of the hydroxylamine bond occurred prior to rearrangement. This electronic restriction to rearrangement is consistent with the findings of others[7,8] and provides an interesting opportunity for further investigation.

In each of the transformations above (Table 2), no indication of a benzoxazolone was observed by 400 MHz ^{1}H NMR spectroscopy of the crude reaction mixture in $CDCl_3$. We therefore heated the rearrangement product **20** (R^1 = Me, R^2 = 4-Me) under microwave irradiation at temperatures between 150 and 200 °C in an attempt to bring about cyclization. The desired cyclization (to give **32**) occurred at temperatures in excess of 160 °C. Unfortunately, at these temperatures **9** partially decomposed prior to rearrangement. We therefore developed a two-stage process to access the target heterocycle from the rearrangement precursor (Table 3). Heating a solution of **9** in toluene (0.33 M) at 150 °C for 4 h followed by heating at 165 °C for 3 h led to the benoxazolone **32** in a pleasing 86% isolated yield (entry 2). Use of a similar two-stage protocol proved effective for a series of substrates (entries 1−8) providing access to benzoxazolones **31**−**38** in high chemical yield (75−87%) in a simple and convenient manner. Reaction of the hydroxylamine **12** (entry 4; 87%) proceeded more efficiently in this two-step protocol than observed in Table 2 (entry 4; 72%) due to incomplete rearrangement of **12** after 3 h at 150 °C.

To further develop the potential of the overall transformation, we examined the conversion of nitroarenes to the corresponding benzoxazolones without purification of the intermediate protected *N*-aryl hydroxylamine. This involved partial reduction of nitrobenzene or 4-nitrotoluene with zinc in the presence of methylchloroformate followed by aqueous workup and heating of the crude product in toluene (150 °C, 4 h, then 160 °C, 3 h). On cooling, the benzoxazolones **31** (65%) and **32** (75%) crystallized directly from the reaction mixture and could be isolated by filtration (see Supporting Information for full details). The simplicity of this procedure and number of commercially available nitroarenes suggest the method should prove amenable to the preparation of arrays of benzoxazolones in high chemical purity.

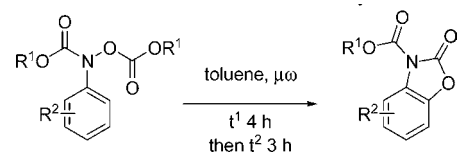
An alternative and equally convenient method for the preparation of the rearrangement precursors involves either palladium[10] or copper[11] catalyzed coupling of protected hydroxylamines with aryl halides. To expand the number

Table 2. Microwave-Assisted Rearrangement of *N*-Aryl Hydroxylamines[a]

entry	substrate	R^1	R^2	product	% yield[b]
1	**9**	Me	4-Me	**20**	88
2	**10**	Me	3-Me	**21**	75[c]
3	**11**	Me	4-Br	**22**	89
4	**12**	Me	4-I	**23**	72
5	**13**	Bn	4-Me	**24**	90[d]
6	**14**	Me	3-CF_3	**25**	0[e]
7	**15**	Me	4-CCH	**26**	82
8	**16**	Me	4-Cl	**27**	91
9	**17**	Me	3-Ph	**28**	67[c]
10	**18**	Me	3-Br	**29**	76[c]
11	**19**	Bn	H	**30**	94[d]

[a] All reactions conducted on 0.5 mmol scale in 1.5 mL of toluene at 150 °C for 3 h. [b] Isolated yield. [c] Product isolated as a 1:1 mixture of regioisomers. [d] Reaction conducted at 160 °C for 3 h. [e] Reaction conducted up to 185 °C.

Table 3. Microwave-Assisted Benzoxazolone Synthesis[a]

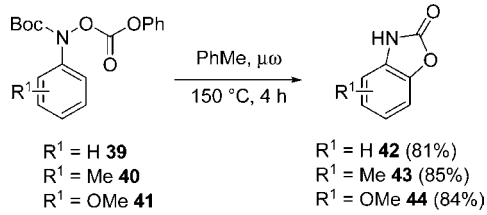


entry	substrate	R^1	R^2	t^1 (°C)	t^2 (°C)	product	% yield[b]
1	**7**	Me	H	150	160	**31**	82
2	**9**	Me	4-Me	150	160	**32**	86
3	**11**	Me	4-Br	150	185	**33**	82
4	**12**	Me	4-I	150	185	**34**	87
5	**13**	Bn	4-Me	160	185	**35**	85
6	**15**	Me	4-CCH	140	160	**36**	75[c]
7	**16**	Me	4-Cl	150	185	**37**	81
8	**19**	Bn	H	160	185	**38**	76

[a] All reactions conducted on a 0.5 mmol scale in 1.5 mL of toluene at t^1 for 4 h then t^2 for 3 h. [b] Isolated yield. [c] Carbonate group removed during cyclization.

of commercially available building blocks that could be used within this chemistry, we prepared the rearrangement precursors **39**−**41** (see Supporting Information for full details). Within these substrates, the Boc protecting group was incorporated to further expand the scope of this transformation. Microwave irradiation of the phenyl carbonates **39**−**41** in toluene at 150 °C for 4 h provided two important alternatives to the overall synthetic procedure (Scheme 2). First, incorporation of a better leaving

Scheme 2. Rearrangement/Cyclization/Deprotection Sequence



R^1 = H **39**
R^1 = Me **40**
R^1 = OMe **41**

R^1 = H **42** (81%)
R^1 = Me **43** (85%)
R^1 = OMe **44** (84%)

group on the carbonate meant that intramolecular cyclization occurred at this lower reaction temperature negating the need for a two-stage rearrangement/cyclization process (cf. Table 3). Second, the Boc protecting group was removed thermally[12] under the reaction conditions providing an advanced building block for further manipulation.[13]

In summary, we have developed an efficient procedure for the preparation of benzoxazolones from nitroarenes or aryl halides. The substrates for rearrangement are easily prepared by either partial reduction of nitroarenes in the presence of a chloroformate or from a palladium-catalyzed coupling of protected hydroxylamines. Heating these products in xylene for 24 h leads to protected 2-amino phenols. Using microwave irradiation, the rearrangement proceeds more efficiently providing the products in good chemical yield. Further heating of the rearranged products provides access to the benzoxazolone nucleus. The overall reaction sequence can be carried out without purification of intermediates and the products purified by simple filtration. The importance of the benzoxazolone pharmacophore together with the robust nature of the synthetic chemistry described suggest this overall strategy will have broad applicability in the preparation of biologically significant molecules based around this central core.

Acknowledgment. The authors thank the EPSRC and GlaxoSmithKline for financial support and the Mass Spectrometry Service, Swansea, for high-resolution spectra.

Supporting Information Available: Analytical data, experimental procedures, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902885J

(10) Porzelle, A.; Woodrow, M. D.; Tomkinson, N. C. O. *Org. Lett.* **2009**, *11*, 233.
(11) Jones, K. L.; Porzelle, A.; Hall, A.; Woodrow, M. D.; Tomkinson, N. C. O. *Org. Lett.* **2008**, *10*, 797.
(12) Rawal, V. H.; Jones, R. J.; Cava, M. P. *J. Org. Chem.* **1987**, *52*, 19.
(13) We believe cyclization occurs prior to Boc removal. See: Dandepally, S. R.; Williams, A. L. *Tetrahedron Lett.* **2009**, *50*, 1071.