Synlett O. Bodero, A. C. Spivey Letter

An Expedient Synthesis of 2-Aryl-1,4-benzoxazin-3-ones via Tandem Anionic Cyclisation/Alkylation Reactions of *N*-Boc-*O*-benzyl-2-aminophenols

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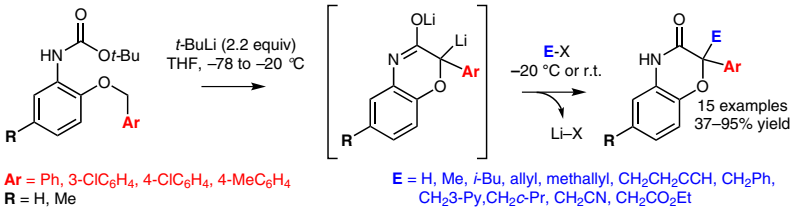

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Abstract A one-pot, tandem anionic cyclization/alkylation reaction of *N*-Boc-*O*-benzylated-2-aminophenols to give 2-aryl-1,4-benzoxazin-3-ones is described. The Boc protecting group plays a crucial role in the process, as the *tert*-butoxide liberated in the cyclisation step facilitates the benzylic deprotonation necessary for the subsequent alkylation. The reaction gives expedient access to a range of substitution patterns in 1,4-benzoxazin-3-ones of potential biological relevance.

Key words 1,4-benzoxazin-3-one, cyclization, alkylation, reagent recycling, DIBOA

Many natural and synthetic 1,4-benzoxazin-3-ones perform useful ecological roles and exhibit interesting bioactivities.[1] For example, 2,4-dihydroxy-1,4-benzoxazin-3-one (DIBOA) and several related compounds which were first isolated from *Zea mays L.*,[2] exhibit phytotoxic and antifungal activity.[3] As a result of agrochemical and pharmaceutical research based on these natural products, the 1,4-benzoxazin-3-one core has served as a template for the development of an array of interesting crop-protection and therapeutic agents displaying useful antifungal,[4] antibacterial,[5] antithrombotic (Factor Xa inhibitory[6]) and antihypertensive (Renin inhibitory[7]) activity (Figure 1).

Various approaches to the synthesis of the 1,4-benzoxazin-3-one core have been developed.[8] The most widely used methods involve the ring-annulation of 2-aminophenols (or 2-nitrophenols, incorporating reduction) with 2-haloacetate derivatives,[6,8,9] various multicomponent variants of these reactions,[10] the ring-closure of *N*-acetyl-2-haloaniline derivatives via intramolecular Buchwald–Hartwig O-arylation,[11] and the ring-annulation of 2-halophenols with 2-haloacetamides via intramolecular Ullmann N-arylation.[12] Although the yields are often good, limited access to appropriately functionalized substrates and/or limited compatibility of required functional groups with the reaction conditions means there is a demand for new approaches to the synthesis of this important ring system.

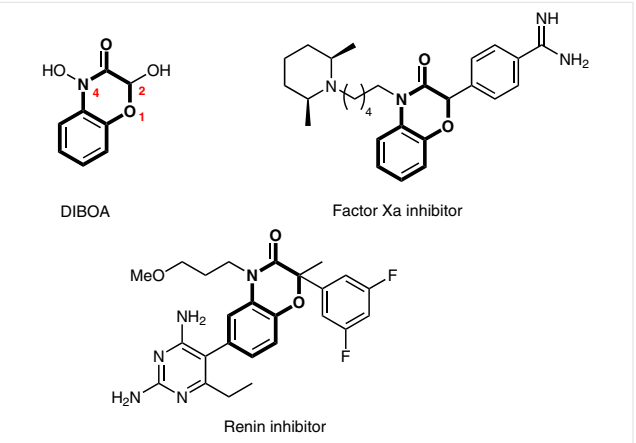
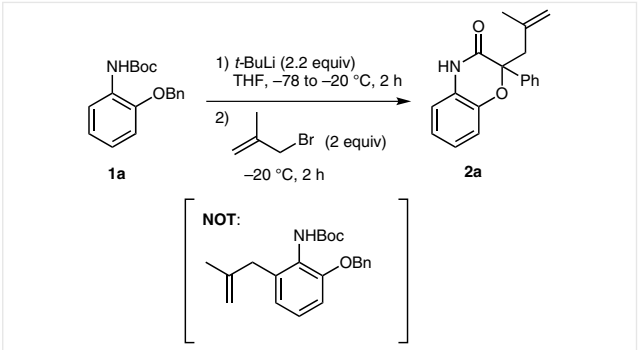


Figure 1 Examples of bioactive compounds based on the 1,4-benzoxazin-3-one scaffold

In the course of some research directed towards the synthesis of 2,6-disubstituted aniline derivatives as components of α-helix mimetics,[13] we had occasion to attempt the directed *ortho* lithiaiton[14] of *N*-Boc-*O*-benzyl-2-aminophenol (**1a**). The plan was to form the dianion, by deprotonation of the *NH*Boc function and the *ortho* ring position using *t*-BuLi (2.2. equiv), and then react this with 3-bromo-2-methylpropene to obtain the C-allylated product. In the event we were surprised to discover that the exclusive product of this reaction was 1,4-benzoxazin-3-one **2a** in 80% yield (Scheme 1).



Scheme 1 Serendipitous tandem 1,4-benoxazin-3-one formation/alkylation reaction

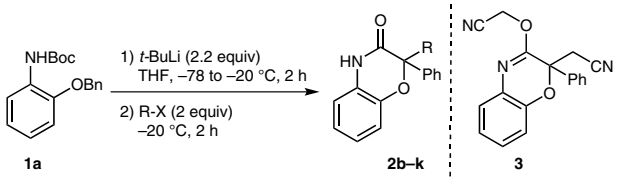
The use of just 2.2 equivalents of *t*-BuLi in this tandem cyclization/alkylation process implicates the *tert*-butoxide generated upon cyclisation as mediating the subsequent benzylic alkylation (vide infra, Scheme 2). The 'waste' *tert*-butoxide generated in the first step is thereby internally recycled to facilitate the next step in an environmentally benign fashion,[15] a concept pioneered by Shibasaki for recycling triphenylphosphine oxide in sequential Wittig alkenylation/asymmetric epoxidation reactions.[16] This 1,4-benzoxazin-3-one synthesis is notable for directly generating a quaternary benzylic stereocentre at C2, as found in several bioactive derivatives[11,17] (e.g. the renin inhibitor[7b] in Figure 1).

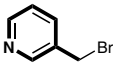
To explore the scope of this transformation we first investigated the use of different electrophiles (Table 1).

Pleasingly, both activated and non-activated electrophiles participated in the reaction. Thus, allyl bromide, benzyl bromide and 3-(bromomethyl)pyridine afforded the expected 1,4-benzoxazinones in good yields under the original conditions (Table 1, entries 1, 5 and 7). Protonation could also be achieved using MeOH (Table 1, entry 3). Isobutyl bromide, 4-butynyl bromide and cyclopropylmethyl bromide afforded excellent yields, provided longer reaction times and higher temperatures were employed (Table 1, entries 2, 4 and 6). By contrast, bromoacetonitrile, ethyl bromoacetate and methyl iodide reacted so rapidly that e.g. when two equivalents of bromoacetonitrile were added the C,O-dialkylated derivative **3** was the only isolated product (Table 1, entry 8). Use of just one equivalent however allowed the formation of the expected product **2h** exclusively (Table 1, entry 9). The same applied when using ethyl bromoacetate (Table 1, entry 10). Methyl iodide was even more reactive and use of 0.9 equivalent was required to obtain exclusively **2j** in excellent yield (Table 1, entry 11).

Next we briefly examined the possibility of introducing substituents in the aromatic rings, using 3-bromo-2-methylpropene as the default alkylating agent (Table 2).

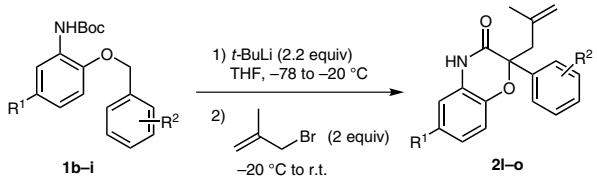
Table 1 Scope of 1,4-Benzoxazin-3-one Formation with Respect to Alkylating Agent RX



Entry[a]	Electrophile (R-X)	Product	Yield (%)
1	CH_2=$CHCH_2$-Br	**2b**	68
2	*i*-Bu-Br[b]	**2c**	77
3	H-OMe	**2d**	95
4	HC≡CCH_2CH_2-Br[b]	**2e**	72
5	Bn-Br[b]	**2f**	63
6		**2g**	89
7		**2h**	85
8	N≡CCH_2-Br	**3**	53
9	N≡CCH_2-Br[c]	**2i**	70
10	EtO_2CCH_2-Br[c]	**2j**	53
11	Me-I[d]	**2k**	93

[a] For general procedure see ref. 18.
[b] Reaction mixture was stirred for 16 h at r.t. after the addition of the electrophile.
[c] Amount of electrophile added was 1 equiv.
[d] Amount of MeI added was 0.9 equiv.

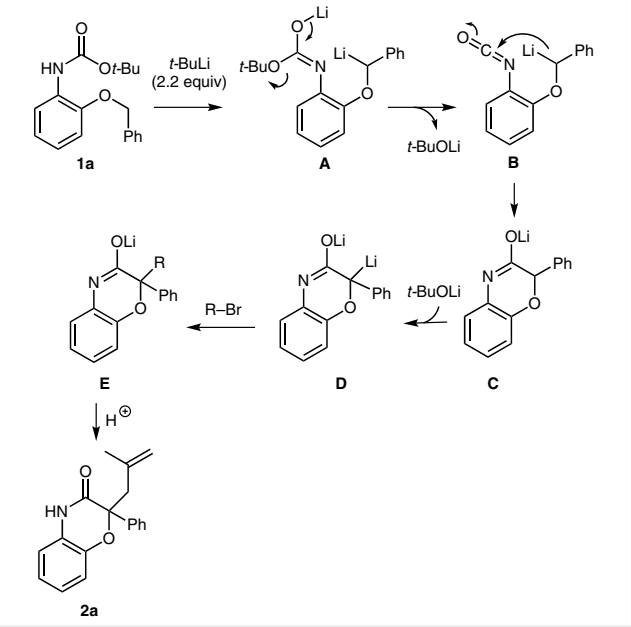
Table 2 Scope of 1,4-Benzoxazin-3-one Formation with Respect to Aryl Substituents



Entry	Substrate	R^1	R^2	Product	Yield (%)
1	**1b**	H	4-Me	**2l**	85
2	**1c**	H	4-Cl	**2m**	75
3	**1d**	H	3-Cl	**2n**	37
4	**1e**	H	2-Me	–	0
5	**1f**	H	4-NO_2	–	0
6	**1g**	H	3,5-$(CF_3)_2$	–	0
7	**1h**	4-Me	H	**2o**	76
8	**1i**	4-Cl	H	–	0

The substrates **1b–i** were readily synthesized from the appropriate 2-aminophenols and benzylic bromides in two steps (see Supporting Information). For the benzylic ring, 4-Me, 4-Cl and 3-Cl groups were tolerated (Table 2, entries 1–3), but 2-Me, 4-NO_2 and 3,5-$(CF_3)_2$ groups were not, even when deploying LDA, NaH or LiHMDS in place of *t*-BuLi; all conditions led to decomposition of the staring material (Table 2, entries 4–6). For the aminophenol ring, just two derivatives were explored: a 4-Me group was tolerated (Table 2, entry 7) but a 4-Cl group led to complex mixtures, apparently due to competing halogen-lithium exchange upon treatment with *t*-BuLi (Table 2, entry 8).

A proposed reaction mechanism for this 1,4-benzoxazin-3-one formation-alkylation reaction is shown below (Scheme 2).

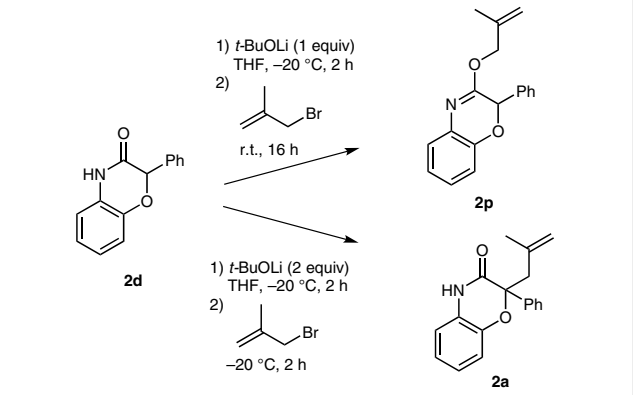


Scheme 2 Proposed reaction mechanism

Compound **1a** reacts with *t*-BuLi to give dilithiated intermediate **A**. Loss of *t*-BuOLi then gives isocyanate **B** which undergoes 6-*endo*-*trig* ring closure to give intermediate **C**. Benzylic deprotonation by the *t*-BuOLi then generates dilithiated intermediate **D** which undergoes alkylation (→ **E**) and protonation to give the product **2a**.

To confirm the feasibility of our proposed mechanism, compound **2d** was dissolved in THF at –20 °C and either one equivalent or two equivalents of *t*-BuOLi was added followed after two hours by 3-bromo-2-methylpropene (Scheme 3).

When one equivalent of *t*-BuOLi was added, a white suspension was formed; after addition of the electrophile no reaction was observed after two hours at –20 °C, but after



Scheme 3 Confirmation that *t*-BuOLi can effect *mono*- and dideprotonation of **2d**

16 hours at room temperature complete conversion to O-alkylated product **2p** was achieved. When two equivalents of *t*-BuOLi were added, an orange suspension was formed; after addition of the electrophile total conversion into C-alkylated product **2a** was achieved after two hours at –20 °C. Clearly, *t*-BuOLi is strong enough as a base to deprotonate intermediate **C** in our proposed mechanism (Scheme 2).

In conclusion, we have reported an expedient method for the synthesis of 2-aryl-1,4-benzoxazin-3-ones via an unusual tandem anionic cyclisation/alkylation reaction of *N*-Boc-*O*-benzyl-2-aminophenols. The substrates for this one-pot transformation are readily prepared in two straightforward steps from commercially available 2-aminophenols and benzylic bromides. The convenience of the procedure allied with the known biological significance of the product class will hopefully make this a useful addition to existing methods for the synthesis of 1,4-benzoxazin-3-ones.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588348.

References and Notes

(1) (a) Macias, F. A.; Marin, D.; Oliveros-Bastidas, A.; Molinillo, J. M. G. *Nat. Prod. Rep.* **2009**, *26*, 478. (b) Hashimoto, Y.; Shudo, K. *Phytochemistry* **1996**, *43*, 551.
(2) Hamilton, R. H.; Bandurski, R. S.; Reusch, W. H. *Cereal Chem.* **1962**, *39*, 107.
(3) Bravo, H. R.; Lazo, W. *J. Agric. Food Chem.* **1996**, *44*, 1569.

(4) (a) Friebe, A.; Vilich, V.; Hennig, L.; Kluge, M.; Sicker, D. *Appl. Environ. Microbiol.* **1998**, *64*, 2386. (b) Macchiarulo, A.; Costantino, G.; Fringuelli, D.; Vecchiarelli, A.; Schiaffella, F.; Fringuelli, R. *Bioorg. Med. Chem.* **2002**, *10*, 3415.
(5) Frechette, R.; Beach, M. PCT Int Appl WO9728167 A1, **1997**.
(6) (a) Dudley, D. A.; Bunker, A. M.; Chi, L.; Cody, W. L.; Holland, D. R.; Ignasiak, D. P.; Janiczek-Dolphin, N.; McClanahan, T. B.; Mertz, T. E.; Narasimhan, L. S.; Rapundalo, S. T.; Trautschold, J. A.; Van Huis, C. A.; Edmunds, J. J. *J. Med. Chem.* **2000**, *43*, 4063. (b) Huang, W.; Zhang, P.; Zuckett, J. F.; Wang, L.; Woolfrey, J.; Song, Y.; Jia, Z. J.; Clizbe, L. A.; Su, T.; Tran, K.; Huang, B.; Wong, P.; Sinha, U.; Park, G.; Reed, A.; Malinowski, J.; Hollenbach, S. J.; Scarborough, R. M.; Zhu, B.-Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 561.
(7) (a) Meguro, K.; Nishikawa, K. Eur. Patent EP0233728 A1, **1987**. (b) Powell, N. A.; Ciske, F. L.; Cai, C.; Holsworth, D. D.; Mennen, K.; Van Huis, C. A.; Jalaie, M.; Day, J.; Mastronardi, M.; McConnell, P.; Mochalkin, I.; Zhang, E.; Ryan, M. J.; Bryant, J.; Collard, W.; Ferreira, S.; Gu, C.; Collins, R.; Edmunds, J. J. *Bioorg. Med. Chem.* **2007**, *15*, 5912.
(8) Ilaš, J.; Anderluh, P. Š.; Dolenc, M. S.; Kikelj, D. *Tetrahedron* **2005**, *61*, 7325.
(9) Özden, S.; Murat Öztürk, A.; Göker, H.; Altanlar, N. *Farmaco* **2000**, *55*, 715.
(10) (a) Xing, X.; Wu, J.; Feng, G.; Dai, W.-M. *Tetrahedron* **2006**, *62*, 6774. (b) Martinand-Lurin, E.; El Kaïm, L.; Grimaud, L. *Tetrahedron Lett.* **2014**, *55*, 5144.
(11) Ylijoki, K. E. O.; Kundig, E. P. *Chem. Commun.* **2011**, *47*, 10608.
(12) Chen, D.; Shen, G.; Bao, W. *Org. Biomol. Chem.* **2009**, *7*, 4067.
(13) Bayly, A. R.; White, A. J. P.; Spivey, A. C. *Eur. J. Org. Chem.* **2013**, *2013*, 5566.
(14) Maggi, R.; Schlosser, M. *J. Org. Chem.* **1996**, *61*, 5430.
(15) (a) Zhou, J.; Zeng, X.-P. In *Multicatalyst System in Asymmetric Catalysis*; John Wiley & Sons: New York, **2014**, 633–670. (b) Zhu, F.; Xu, P.-W.; Zhou, F.; Wang, C.-H.; Zhou, J. *Org. Lett.* **2015**, *17*, 972.
(16) Kinoshita, T.; Okada, S.; Park, S.-R.; Matsunaga, S.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 4680.
(17) Brindisi, M.; Gemma, S.; Alfano, G.; Kshirsagar, G.; Novellino, E.; Campiani, G.; Butini, S. *Tetrahedron Lett.* **2013**, *54*, 5387.
(18) **General Procedure; Anionic Cyclisation/Alkylation Reaction**: To a solution of the appropriate *N*-Boc-*O*-benzyl-2-aminophenol (0.3 mmol) in anhyd THF (1 mL) under nitrogen atmosphere cooled at –78 °C, a solution of *t*-BuLi was added dropwise (1.7 M in pentane, 0.39 mL, 0.66 mmol). The solution immediately turned orange. It was stirred at –78 °C for 10 min, then 2 h at –20 °C. Then the corresponding electrophile was added (0.6 mmol) and the resulting mixture was stirred for an additional 2 h at 20 °C before being quenched with H_2O (5 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts washed with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$ and filtered. The product was purified by flash chromatography eluting with hexane–EtOAc (9:1 → 8:2). Data for selected products (for all data, see Supporting Information) follows.
2a: mp 110–111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.88 (br s, 1 H), 7.54 (d, *J* = 8.3 Hz, 2 H), 7.20–7.35 (m, 3 H), 7.09–7.18 (m, 1 H), 7.00 (td, *J* = 7.8, 1.5 Hz, 1 H), 6.90 (td, *J* = 7.7, 1.3 Hz, 1 H), 6.73 (dq, *J* = 7.9, 1.4 Hz, 1 H), 4.65–5.13 (m, 2 H), 3.21 (d, *J* = 14.7 Hz, 1 H), 2.84 (d, *J* = 14.7 Hz, 1 H), 1.81 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.3, 142.9, 140.5, 139.0, 128.3, 128.0, 126.1, 125.6, 124.1, 122.4, 120.7, 117.5, 115.5, 115.4, 84.7, 46.8, 28.7, 28.3, 24.5. HRMS (ES): *m*/*z* [M + H$^+$] calcd for $C_{18}H_{18}NO_2$: 280.13318; found: 280.1335. IR: 1680, 1502, 1448, 1370, 1155, 1057 cm^{-1}.
2g: mp 150–155 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.56 (s, 1 H), 7.56 (d, *J* = 6.8 Hz, 2 H), 7.22–7.36 (m, 3 H), 7.17 (d, *J* = 7.9 Hz, 1 H), 7.02 (td, *J* = 7.8, 1.4 Hz, 1 H), 6.91 (td, *J* = 7.8, 1.4 Hz, 1 H), 6.81 (dd, *J* = 7.8, 1.4 Hz, 1 H), 2.38 (dd, *J* = 14.5, 6.8 Hz, 1 H), 2.12 (dd, *J* = 14.5, 6.8 Hz, 1 H), 0.98–1.08 (m, 1 H), 0.35–0.57 (m, 2 H), 0.19–0.33 (m, 1 H), 0.00–0.08 (m, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.2, 143.3, 139.3, 128.3, 127.9, 126.3, 125.7, 124.4, 122.2, 117.3, 115.6, 84.9, 44.6, 6.0, 4.6, 4.4. HRMS (ES): *m*/*z* [M + H$^+$] calcd for $C_{18}H_{18}NO_2$: 280.1338; found: 280.1345, IR: 1688, 1502, 1428, 1368, 1124, 1045 cm^{-1}.
2h: mp 123–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.35 (s, 1 H), 8.54 (s, 1 H), 8.40–8.50 (m, 1 H), 7.58 (d, *J* = 12 Hz, 1 H), 7.46 (dd, *J* = 6.1, 1.8 Hz, 2 H), 7.22–7.35 (m, 3 H), 7.06–7.18 (m, 2 H), 6.97 (ddd, *J* = 7.9, 6.1, 1.8 Hz, 1 H), 6.88 (ddd, *J* = 7.9, 6.1, 1.8 Hz, 1 H), 6.72 (dt, *J* = 7.9, 1.8 Hz, 1 H), 3.72 (dd, *J* = 14.1, 1.6 Hz, 1 H), 3.40 (dd, *J* = 14.1, 1.6 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.6, 152.1, 147.9, 142.7, 138.7, 138.0, 131.3, 128.5, 128.4, 126.1, 125.7, 124.1, 122.8, 122.6, 117.5, 115.5, 84.1, 43.0, 28.2. HRMS (ES): *m*/*z* [M + H$^+$] calcd for $C_{20}H_{17}N_2O_2$: 317.1290; found: 317.1302. IR: 1682, 1502, 1448, 1372, 1128, 1031 cm^{-1}.