Synthesis of Benzoxazines, Quinazolines and 4*H*-Benzo[*e*][1,3]thiazine by ANRORC Rearrangements of 1,2,4-Oxadiazoles

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Abstract: 1,2,4-Oxadiazoles undergo ANRORC (*a*ddition of *nu*cleophile, *ring-o*pening and *ring-c*losure) rearrangements upon reaction with excess of *n*-butyllithium to give benzoxazines, benzothiazines, and quinazolines in good yields under mild conditions.

Key words: N,O-heterocycles, rearrangements, benzoxazines, quinazolines, benzothiazines

1,2,4-Oxadiazole is one of the least aromatic five-membered heterocyclic systems (aromaticity index $I_5 = 39$ or $I_A = 48$[1a,b]). Its derivatives are of interest (i) in medicinal chemistry as pharmacophores simulating a metabolically stable isostere of an ester unit;[2a] (ii) as components in drug molecules, including Perebron,[2b] and Libexin;[2c] (iii) in materials science in the formulation of ionic liquids, liquid crystals, and organic light emitting diodes (OLEDs),[2d–f] and (iv) in synthesis because of their high reactivity and tendency to undergo the Boulton–Katritzky[3a–d] and ANRORC (*a*ddition of *n*ucleophile, *r*ing-*o*pening and *r*ing-*c*losure)[3e] molecular rearrangements.[3f,g]

ANRORC reactions allow valuable synthetic ring transformations of heterocyclic systems to be achieved and have been used by Vivona and co-workers to synthesize 1,2,4-triazoles,[4a] 1,2,4-oxadiazoles,[4b] 1,2,4-triazines,[4c,d] 1,2,4-oxadiazinones,[4e] and indazoles.[4f] The ANRORC approach was initially limited to 1,2,4-oxadiazoles with strongly electron-withdrawing fluorinated groups attached to C-5, but was recently extended to 1,2,4-oxadiazoles lacking electron-withdrawing groups at C-5.[4g] We now disclose ANRORC type transformations of 1,2,4-oxadiazoles into 2,4-substituted quinazoline, and 4*H*-benzo[*e*][1,3]thiazine derivatives.

We prepared 1,2,4-oxadiazoles **3a–g** from *N*-acylbenzotriazoles **1a–e** and (*Z*)-*N*′-hydroxybenzimidamides **2a–c** in yields of 70–88% (Table 1) following a published procedure.[5a] 2-(3-Substituted 1,2,4-oxadiazol-5-yl)anilines **5a–d** were prepared from isatoic anhydride (**4**) and (*Z*)-*N*′-hydroxybenzimidamides **2a**, **2b**, **2d**, and **2e** (Table 2), following the procedure of Nagahara.[5b]

Table 1 Synthesis of 1,2,4-Oxadiazoles **3a–g**

Product	R^1	R^2	Yield (%)
3a	Ph	Ph	86
3b	2-HOC$_6$H$_4$	4-MeC$_6$H$_4$	88
3c	2-HOC$_6$H$_4$	Ph	76
3d	2-HOC$_6$H$_4$	4-O$_2$NC$_6$H$_4$	81
3e	3-HO-2-naphthyl	Ph	82
3f	2-HO-1-naphthyl	Ph	79
3g	2-HSC$_6$H$_4$	Ph	70

Table 2 Synthesis of 1,2,4-Oxadiazoles **5a–d**

Product	R^1	Yield (%)
5a	Ph	65
5b	4-MeC$_6$H$_4$	62
5c	Me	89
5d	*i*-Pr	86

It is known that *n*-butyllithium adds to C-5 of a 1,2,4-oxadiazole ring (the most electrophilic site) initiating a cascade of ring opening/ring closing rearrangements (ANRORC type).[6] We have now studied two-step rearrangements of 1,2,4-oxadiazoles using *n*-butyllithium (2 to 4 equiv) as an external nucleophile, and potential O, S, and N nucleophiles attached to position-5. We also examined the behavior of the 1,2,4-oxadiazole ring in the presence of Grignard reagents as external nucleophiles.

Compounds **6a**, **6b**, **7a** and **7b** were prepared by applying Srivastava's procedure.[6] As reported,[6] addition of *n*-butyllithium (1 equiv) to 3,5-diphenyl-1,2,4-oxadiazole (**3a**) at
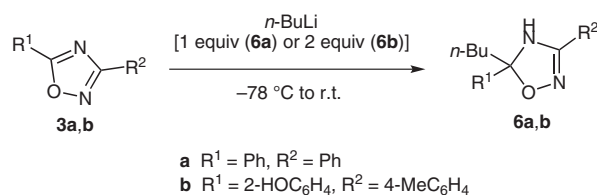
–78 °C gave 5-butyl-3,5-diphenyl-4,5-dihydro-1,2,4-oxa-diazole (**6a**) in 60% yield. Similarly, addition of *n*-butyl-lithium (2 equiv) to 2-[3-(4-tolyl)-1,2,4-oxadiazol-5-yl]phenol (**3b**) gave 2-[5-butyl-3-(4-tolyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl]phenol (**6b**) in 75% yield (Scheme 1).

**Scheme 1**   Monoaddition products of 1,2,4-oxadiazoles **3a** and **3b**

As also reported by Srivastava et al.,[6] adding four equivalents of *n*-butyllithium to 2-(3-phenyl-1,2,4-oxadiazol-5-yl)phenol (**3c**) under the same reaction conditions gave the rearranged product 4,4-dibutyl-2-phenyl-4*H*-benzo[*e*][1,3]oxazine (**7a**) in 40% yield (Scheme 2). The scope of the reaction was explored further by reacting *n*-butyllithium with 2-[3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl]phenol (**3d**), which contains a strong electron-withdrawing group (4-NO₂) attached to C-3 of the 1,2,4-oxa-diazole, however this procedure led to decomposition and to the formation of an intractable mixture.

Reaction of 3-(3-phenyl-1,2,4-oxadiazol-5-yl)naphtha-lene-2-ol (**3e**) with four equivalents of *n*-butyllithium in tetrahydrofuran at –78 °C, gave the novel compound 4,4-dibutyl-2-phenyl-4*H*-naphtho[2,3-*e*][1,3]oxazine (**7b**) in 50% yield. However, subjecting 1-(5-phenyl-1,2,4-oxadi-azol-3-yl)naphthalen-2-ol (**3f**) to the same reaction conditions led to decomposition of the starting materials, probably due to the steric hindrance imparted by the second phenyl group in **3f**.

The methodology was extended to the synthesis of 4*H*-benzo[*e*][1,3]thiazine and 2,4-disubstituted quinazolines by ANRORC rearrangements of 1,2,4-oxadiazoles containing potentially nucleophilic sulfur and nitrogen groups at the 5-position. Thus, treatment of 2-(3-phenyl-1,2,4-oxadiazol-5-yl)benzenethiol (**3g**) with *n*-butyllithi-um (4 equiv) in tetrahydrofuran at –78 °C gave 4-butyl-2-phenyl-4*H*-benzo[*e*][1,3]thiazine (**7c**; Scheme 2). When 2-(3-substituted 1,2,4-oxadiazol-5-yl)anilines **5a–d**, with aromatic substituents at C-3, were treated with *n*-butyl-lithium (4 equiv), 2,4-disubstituted quinazolines **8a** and **8b** were formed in 25 and 75% yields, respectively. With aliphatic substituents at C-3 (**5c** and **5d**), the reaction gave unidentified products. The significant difference in yields for the formation of **5a** (25%) and **5b** (75%) occurs because the donating methyl group reduces the electrophi-licity of the 1,2,4-oxadiazole ring at C-3. Consequently, nucleophilic attack by a carbon nucleophile is selective for C-5, which decreases the amount of side products formed and enhances the yields. This hypothesis is supported by the result obtained when 2-[3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl]phenol (**3d**) was reacted with *n*-butyllithium; under these conditions, the reaction resulted in decomposition because the electron-withdrawing group (NO₂) increased the electrophilicity of C-3 and led to attack of the nucleophile on two different carbons, resulting in a loss of selectivity. Moreover, the reaction failed when aliphatic substituents (**5c** and **5d**) were used because aliphatic substituents do not stabilize the intermediate.

Finally, the use of Grignard reagents as carbon nucleophiles was examined by reacting methyl magnesium bromide and ethynyl magnesium bromide with 2-(3-phenyl-1,2,4-oxadiazol-5-yl)phenol (**3b**); however, no reaction was observed under a range of reaction conditions.

The proposed mechanism of this rearrangement (Scheme 3) was initially suggested by Srivastava et al.[6] and is presented here with some modification to explain
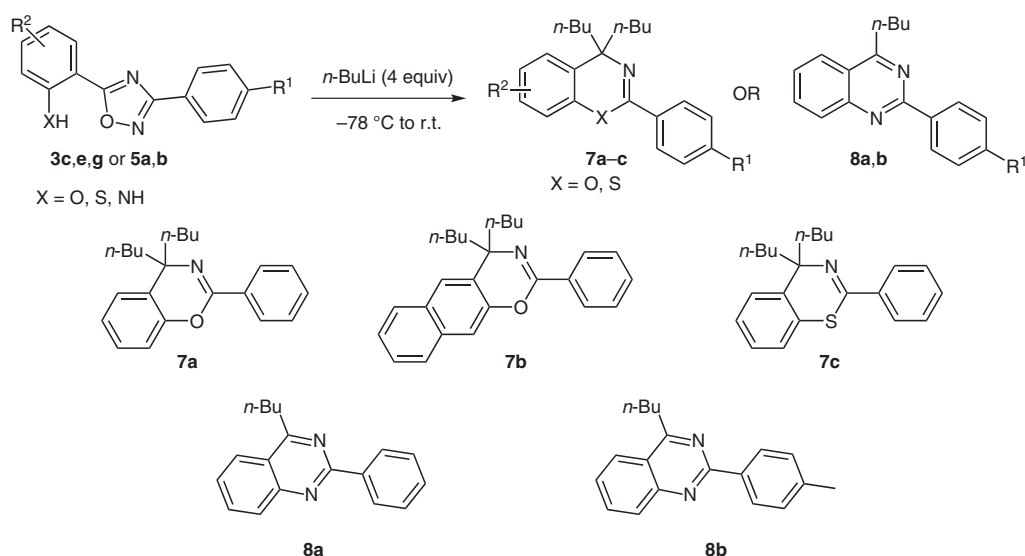
Scheme 2   ANRORC rearrangement of 1,2,4-oxadiazoles **3c**, **3e**, **3g**, **5a** and **5b**
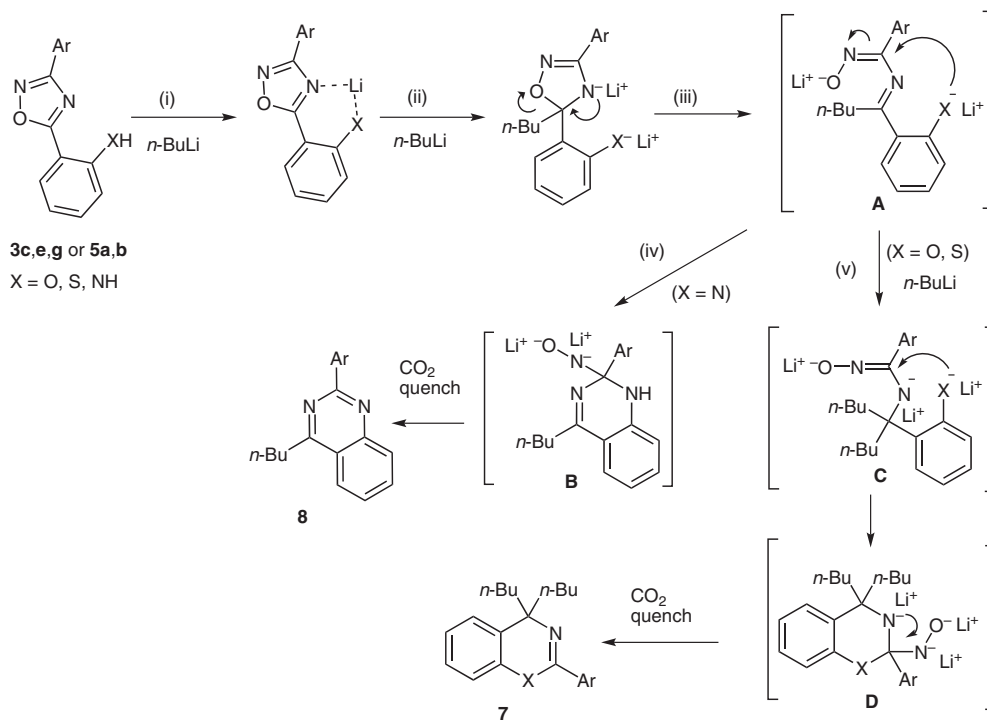
Scheme 3 Modified reaction mechanism for ANRORC rearrangement based on the mechanism proposed by Srivastava et al.[6]

the rearrangement in cases involving nitrogen and sulfur nucleophiles. The proposed mechanism involves the following steps: (i) The first mole of *n*-butyllithium acts as a base to remove a proton from the 1,2,4-oxadiazole moiety and the Li⁺ ion coordinates to N-4 of 1,2,4-oxadiazole ring. (ii) The second mole of *n*-butyllithium acts as a nucleophile and adds to the most electrophilic site, C-5. (iii) Ring opening occurs to give intermediate **A**. (iv) Ring opening is followed by ring closure through nucleophilic attack by a nitrogen atom to form intermediate **B**, which gives quinazoline **9**; this step is driven by the stabilization gained from forming an aromatic ring. (v) With oxygen or sulfur as the internal nucleophiles, ring opening is followed by addition of another mole of *n*-butyllithium to give intermediate **C**, which undergoes ring closure to form intermediate **D** and eventually gives benzoxazine or benzothiazine **7a–c**.

The mechanism helps to explain our experimental results: (i) At least three moles of *n*-butyllithium are required to open the ring and stabilize the anion formed and explains why only one or two moles gave the monoaddition product in the case of **3a** and **3b**. (ii) The presence of a strong electron-withdrawing group in the *para* position of the substituent at C-3 of the oxadiazole ring makes this carbon atom prone to nucleophilic attack in addition to C-5, which leads to an intractable mixture as found with **3d**. (iii) The presence of a bulky group at C-5 hinders nucleophilic attack at the oxadiazole ring as in the case of **3f**. (iv) Grignard reagents did not work as carbon nucleophiles in the case of **3b**, probably due to the larger size of Mg²⁺ (radius = 150 pm) relative to Li⁺ (radius = 90 pm), with the smaller cation being able to stabilize the six-mem-

bered transition state, thus activating C-5 for nucleophilic attack.

In conclusion, 1,2,4-oxadiazoles with potential nucleophiles at the 5-position were activated using *n*-butyllithium to promote ANRORC rearrangement leading to 2,4-disubstituted quinazolines and 4*H*-benzo[*e*][1,3]thiazine. This novel synthetic protocol provides easy access to these important heterocyclic ring systems via ANRORC rearrangements of the 1,2,4-oxadiazoles.

Melting points were determined with a capillary melting point apparatus equipped with a digital thermometer and are uncorrected. Reactions were carried out using dried solvents under an argon atmosphere. Glassware was flame-dried and allowed to cool under a stream of argon. ¹H and ¹³C NMR spectra were recorded at ambient temperature with a Varian Gemini instrument, operating at 300 and 75 MHz, respectively.

Preparation of 7a–c, 8a, and 8b; General Procedure
The corresponding 1,2,4-oxadiazole (0.5 mmol) was dissolved in anhydrous THF (2 mL). The resulting mixture was cooled to –78 °C under an argon atmosphere and *n*-BuLi (1.6 M in hexanes, 1.25 mL, 2.00 mmol) was added dropwise over 20 min. The resulting mixture was stirred for an additional 30 min at –78 °C, and then allowed to warm to r.t. The product was purified by column chromatography (EtOAc–hexanes, 1:10) to give the pure product.

4,4-Dibutyl-2-phenyl-4*H*-benzo[*e*][1,3]oxazine (7a)[6]
Yield: 64 mg (40%); colorless oil.

¹H NMR (300 MHz, CDCl₃): δ = 8.10 (dd, *J* = 7.5, 1.7 Hz, 2 H), 7.48–7.42 (m, 3 H), 7.21–7.18 (m, 1 H), 7.13 (d, *J* = 0.6 Hz, 1 H), 7.11 (t, *J* = 0.8 Hz, 1 H), 7.00 (dt, *J* = 7.8, 0.8 Hz, 1 H), 1.87–1.81 (m, 4 H), 1.27–1.16 (m, 7 H), 0.99–0.85 (m, 2 H), 0.78 (t, *J* = 7.0 Hz, 6 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 149.7, 132.8, 130.8, 128.9, 128.3, 127.6, 127.5, 125.7, 124.7, 124.6, 115.3, 59.3, 44.5, 26.8, 23.1, 14.2, 14.1.

Anal. Calcd for C$_{22}$H$_{27}$NO: C, 82.20; H, 8.47; N, 4.36. Found: C, 81.95; H, 8.83; N, 4.21.

4,4-Dibutyl-2-phenyl-4*H*-naphtho[2,3-*e*][1,3]oxazine (7b)

Yield: 93 mg (50%); brown microcrystals; mp 76.0–77.0 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.17–8.14 (m, 2 H), 7.80–7.43 (m, 2 H), 7.40 (s, 1 H), 7.37–7.22 (m, 7 H), 2.00–1.92 (m, 4 H), 1.32–1.17 (m, 7 H), 1.15–0.93 (m, 3 H), 0.72 (t, *J* = 3.8 Hz, 6 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 150.4, 148.2, 133.1, 132.9, 131.4, 130.8, 128.3, 127.9, 127.6, 127.1, 126.6, 126.3, 124.8, 124.7, 110.7, 59.7, 45.1, 26.7, 23.1, 14.2.

Anal. Calcd for C$_{26}$H$_{29}$NO: C, 84.05; H, 7.87; N, 3.77. Found: C, 84.35; H, 8.18; N, 3.45.

4,4-Dibutyl-2-phenyl-4*H*-benzo[*e*][1,3]thiazine (7c)

Yield: 34 mg (20%); yellow oil.

^{1}H NMR (300 MHz, CD$_2$Cl$_2$): δ = 8.05–8.04 (m, 2 H), 8.03–7.51 (m, 5 H), 7.49–7.20 (m, 4 H), 5.80 (t, *J* = 7.6 Hz, 1 H), 2.57 (q, *J* = 7.3 Hz, 3 H), 1.56 (sext, *J* = 7.5 Hz, 4 H), 1.25 (m, 2 H), 0.97 (t, *J* = 7.5 Hz, 4 H), 0.82 (m, 2 H).

^{13}C NMR (75 MHz, CD$_2$Cl$_2$): δ = 141.2, 138.1, 131.7, 129.6, 129.1, 128.7, 128.3, 127.7, 127.2, 126.8, 125.5, 124.7, 40.7, 29.4, 23.7, 23.5, 14.3.

HRMS (MALDI-TOF): *m/z* [M + H]$^+$ calcd for C$_{22}$H$_{27}$NS: 338.1898; found: 338.1903.

4-Butyl-2-phenylquinazoline (8a)

Yield: 33 mg (25%); yellow oil.

^{1}H NMR (300 MHz, CD$_2$Cl$_2$): δ = 8.57–8.54 (m, 2 H), 8.07 (ddd, *J* = 8.3, 1.4, 0.7 Hz, 1 H), 7.96 (ddd, *J* = 8.3, 1.4, 0.7 Hz, 1 H), 7.78 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1 H), 7.51 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1 H), 7.46–7.29 (m, 3 H), 3.26 (t, *J* = 7.9 Hz, 2 H), 1.91–1.81 (m, 2 H), 1.46 (sext, *J* = 7.3 Hz, 2 H), 0.94 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, CD$_2$Cl$_2$): δ = 172.2, 160.2, 151.2, 139.0, 133.9, 130.8, 129.7, 129.0, 127.3, 125.3, 123.1, 34.8, 31.2, 23.3., 14.4.

HRMS (MALDI-TOF): *m/z* [M + H]$^+$ calcd for C$_{18}$H$_{18}$N$_2$: 263.1543; found: 263.1557.

4-Butyl-2-(4-tolyl)quinazoline (8b)

Yield: 104 mg (75%); green solid; mp 73.0–74.0 °C.

^{1}H NMR (300 MHz, CD$_2$Cl$_2$): δ = 8.44 (d, *J* = 8.2 Hz, 2 H), 8.04 (dddd, *J* = 8.4, 1.4, 0.7, 0.7 Hz, 1 H), 7.92 (dddd, *J* = 8.4, 1.2, 0.6, 0.6 Hz, 1 H), 7.75 (ddd, *J* = 8.5, 7.0, 1.6 Hz, 1 H), 7.47 (ddd, *J* = 8.1, 6.8, 1.1 Hz, 1 H), 7.24 (d, *J* = 8.0 Hz, 2 H), 3.25–3.20 (m, 2 H), 2.35 (s, 3 H), 1.91–1.81 (m, 2 H), 1.44 (sext, *J* = 7.4 Hz, 2 H), 0.93 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (75 MHz, CD$_2$Cl$_2$): δ = 172.0, 151.2, 141.2, 136.3, 133.8, 129.7, 129.6, 128.9, 127.0, 125.3, 123.0, 34.8, 31.2, 23.3, 21.8, 14.3.

Anal. Calcd for C$_{19}$H$_{20}$N$_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 83.39; H, 7.40; N, 9.94.

Supporting Information

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