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Oxidative Radical Skeletal Rearrangement Induced by Molecular Oxygen: Synthesis of Quinazolinones

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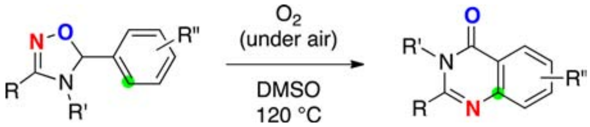
ABSTRACT



Oxidative skeletal rearrangement of 5-aryl-4,5-dihydro-1,2,4-oxadiazoles into quinazolinones is induced by molecular oxygen (under a dry air atmosphere) that likely proceeds via transient iminyl radical species. Concise syntheses of biologically active quinazolinone derivatives were demonstrated using the present strategy.

Nitrogen-containing heterocycles (azaheterocycles) are an omnipresent component of numerous natural alkaloids and potent pharmaceutical drugs.[1] Among various azaheterocycles, quinazolinone derivatives show a broad spectrum of potent biological activities.[2] Typically, the quinazolinone structures are constructed using anthranilic acids or their derivatives via the sequence of their acylation and condensation, which normally require strong acidic or basic reaction conditions.[3] While several efficient methods have recently been developed to assemble quinazolinone frameworks with Pd or Cu catalysts,[4] there remains a demand for robust processes to construct these azaheterocyclic scaffolds from readily available building blocks in atom- and step-economical manners.

Free-radical mediated reactions are powerful tools for construction of various carbon–carbon and carbon–heteroatom bonds.[5] Rational design of substrates and reaction conditions would enable control of the highly reactive radical species, leading to the formation of desired target molecules with high efficiency. The group of Malacria, Fensterbank, Lacôte, and Courillon has recently developed an elegant strategy to assemble quinazolinone structures by a radical-cascade reaction of *N*-benzoylcyanamides bearing iodo-aryl/alkenyl tethers or azido-alkyl tethers (Scheme 1A).[6] The reaction mechanism includes generation of cyclic iminyl radicals **A** followed by radical addition of **A** to the intramolecular aromatic moiety, while this method requires stoichiometric use of toxic organotin compounds (Bu_3SnH). Herein, we report oxidative radical skeletal rearrangement of readily available 5-aryl-4,5-dihydro-1,2,4-oxadiazoles **1** into quinazolinones **2** via iminyl radicals **A**, which is carried out just by heating **1** *under a dry air atmosphere in DMSO without any other additives* (Scheme 1B).

[†] Y.-F.W. and F.-L.Z. contributed equally.

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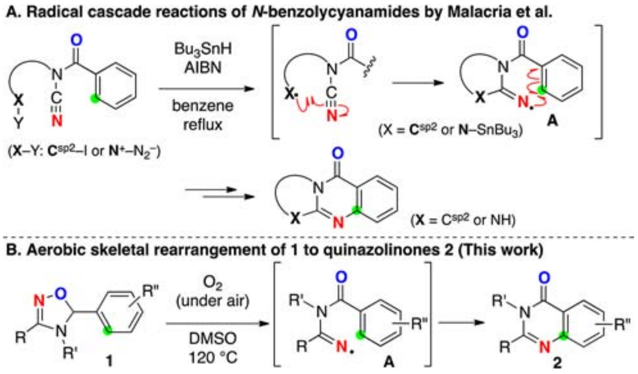
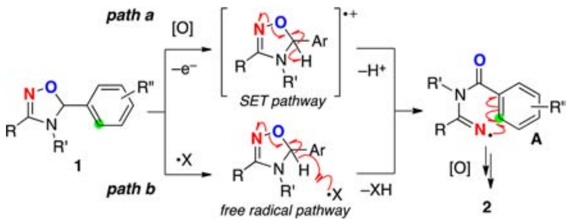
Scheme 1. Free-Radical Approaches to Quinazolinones



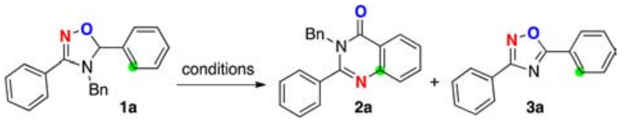
Scheme 2. Oxidative Generation of Iminyl Radicals **A** from **1**



Our reaction design was guided by the potential of tin-free radical-mediated molecular transformation.[7] In this context, oxidative radical skeletal rearrangement of 5-aryl-4,5-dihydro-1,2,4-oxadiazoles **1** into quinazolinones **2** was envisioned via the iminyl radical intermediates **A** (Scheme 2). For generation of iminyl radicals **A**, two possible scenarios were speculated upon: (*path a*) via single-electron oxidation of **1** followed by homolytic N–O bond cleavage of the resulting cation radical and subsequent deprotonative C═O bond formation to generate iminyl radical **A**; (*path b*) via H radical abstraction with an external radical source (X$^\bullet$) and subsequent homolytic N–O bond cleavage[8] to give iminyl radical **A**. The resulting iminyl radical **A** then undergoes radical addition onto the intramolecular aryl moiety,[9] which is followed by oxidative aromatization to afford quinazolinones **2**.[10]

With our hypothesis depicted in Scheme 2, we commenced our investigation with the reactions of dihydrooxadiazole **1a** using a series of oxidants. The reaction of **1a** with DDQ in DMSO at 100 °C gave no desired quinazolinone **2a** but oxadiazole **3a** exclusively in 82% yield via debenzylation and aromatization (Table 1, entry 1), while that with 1,4-benzoquinone did not provide any product at all (entry 2). It was found that oxidation of **1a** with PhI(OAc)$_2$ provided quinazolinone **2a**[11] in 29% yield in addition to the formation of 1,2,4-oxadiazole **3a** (60% yield) (entry 3). Interestingly, treatment of **1a** with TEMPO resulted in selective formation of quinazolinone **2a** without yielding oxadiazole **3a**, although the reaction rate was very slow (entry 4). It is worthy to note that heating of **1a** in DMSO at 100 °C under an O$_2$ atmosphere rendered the process more efficient for the synthesis of quinazolinone **2a** (entry 5). A higher reaction temperature (120 °C) allowed the aerobic reaction to complete to afford **2a** as a sole product in 73% yield (entry 6). The yield of **2a** was further improved to 84% by conducting the reaction under a dry air atmosphere (0.21 atm of O$_2$) (entry 7). Screening of the solvents revealed that DMF and DMA also performed well for this transformation, while nonpolar solvents such as toluene did not work at all (entries 8–10). Heating of **1a** in DMSO at 120 °C under an Ar atmosphere gave **2a** only in 2% yield with recovery of **1a** (entry 11).

Table 1. Optimization of Reaction Conditions[a]



entry	oxidant (equiv)	solvent	temp (°C)	time (h)	yield (%)[b] 2a	3a
1	DDQ (2)	DMSO	100	0.3	0	82
2	BQ (2)	DMSO	100	24	0 (85)[c]	0
3	PhI(OAc)$_2$ (2)	DMSO	100	20	29	60
4	TEMPO (3)	DMSO	100	48	16 (76)[c]	0
5	O$_2$ (1 atm)	DMSO	100	47	47 (41)[c]	0
6	O$_2$ (1 atm)	DMSO	120	28	73	0
7	**dry air (1 atm)**	**DMSO**	**120**	**28**	**84**	**0**
8	dry air (1 atm)	DMF	120	32	81	0
9	dry air (1 atm)	DMA	120	32	76	0
10	dry air (1 atm)	toluene	110	21	0 (95)[c]	0
11[d]	–	DMSO	120	24	2 (83)[c]	0

[a] The reactions were carried out using 0.3 mmol of **1a** in solvents (0.1 M). [b] Isolated yields. [c] Recovery yield of **1a**. [d] The reaction was conducted under an Ar atmosphere. Bn = benzyl; DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; BQ = *p*-benzoquinone; TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl.

The scope of the quinazolinone synthesis was next explored with the optimized aerobic reaction conditions (Scheme 3).[12] By varying the substituent R^1, both electron-rich and -deficient benzene rings (**2b**–**d**) as well as nitrogen-heteroaromatic (pyridyl and indolyl) motifs (**2e**–**f**) could be installed. Moreover, primary and secondary alkyl groups were tolerated in the present process (**2g**–**h**). Instead of a benzyl group as R^2, the 4-methoxybenzyl group (**2i**) and

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(7) For reviews on tin-free radical reactions, see: (a) Renaud, P. *Chimia* **2012**, *66*, 361. (b) Kim, S.; Kim, S. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 809. (c) Quiclet-Sire, B.; Zard, S. Z. *Chem.*—*Eur. J.* **2006**, *12*, 6002.

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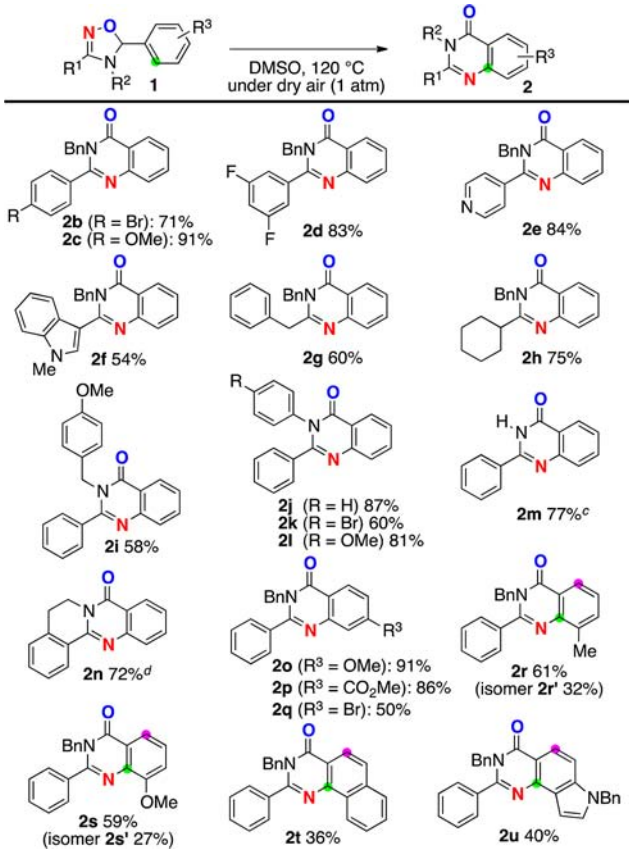
(11) For assigments of the structures of **2a**, **2s′**, **2t**, **2u**, **2v**, **2w**, **4w**, and **5w** by X-ray crystallographic analysis, see the SI.

(12) See the SI for preparation of **1**.

several benzene rings (**2j**–**2l**) could be installed. It is noteworthy that the reaction of **1m** bearing a hydrogen atom as R^2 also proceeded very smoothly to give quinazolinone **2m** in 77% yield without forming 1,2,4-oxadiazole. Facile construction of polycyclic quinazolinone **2n** could be achieved by the present strategy. As the substituents R^3 on the aminated benzene ring, both electron-donating (**2o**) and -withdrawing (**2p**) groups at the *para* position were tolerated while the substrate bearing a C–Br bond provided a moderate yield (**2q**, 50%). In the case of substrates **1r** and **1s** bearing a *meta*-substituted benzene ring, regioisomeric mixtures were obtained where the sterically hindered C–H bond was preferentially aminated (marked in green) to provide **2r** and **2s**, respectively. From the reaction of **1t** with a 2-naphthyl moiety, only quinazolinone **2t** formed via amination on the α-carbon of the naphthyl moiety (marked in green) could be isolated, although the yield was moderate. Similarly, cyclization with a 5-indolyl moiety was observed only at its C(4) (marked in green) to afford **2u** in 40% yield.

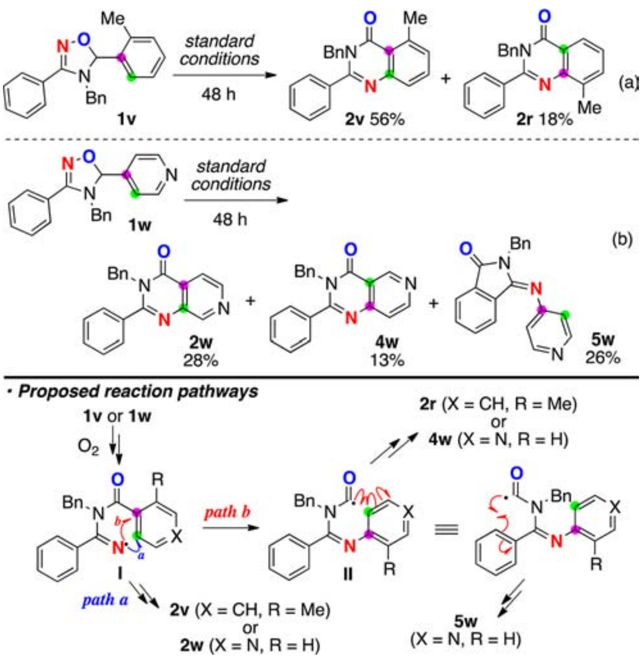
Scheme 3. Substrate Scope[a]



[a] Unless otherwise noted, the reactions were carried out using 0.3 mmol of **1** in DMSO (0.1 M) at 120 °C under a dry air atmosphere for 5.5–48 h. [b] Isolated yields. [c] The reaction was conducted at 100 °C for 2 h. [d] Synthesis of **2n** was conducted starting from 3,4-dihydroisoquinoline-1(2*H*)-thione via formation of amidoxime, acetal exchange with benzaldehyde dimethyl acetal, and aerobic quinazolinone formation (see the Supporting Information (SI) for more details).

The reaction of substrate **1v** bearing a 2-methylphenyl moiety provided the desired quinazolinone **2v** in 54% yield along with the unexpected formation of quinazolinone **2r** in 18% yield (Scheme 4a). Similarly, 4-pyridyl substrate **1w** led to the formation of not only the desired quinazolinone **2w** but also another regioisomeric quinazolinone **4w** and 3-(4-pyridiylimino)isoindolinone **5w** in 28, 13, and 26% yields, respectively (Scheme 4b). The unexpected formation of **2r** from **1v** as well as **4w** and **5w** from **1w** could be rationalized by the presence of carbamoyl radical **II** that might be generated by aryl group migration (*path b*) via attack of putative iminyl radical **I** to the *ipso*-carbon (marked in purple).[13,14] The resulting carbamoyl radical **II** could add to the migrated aryl moiety to afford **2r** or **4w**, while its addition to the phenyl part could generate iminoisoindolinone **5w**.

Scheme 4. Reactions of **1v** and **1w**



To further demonstrate the potential utility of this aerobic method, concise syntheses of biologically active compounds bearing the quinazoline core were carried out from readily available starting materials. An indoloquinazoline alkaloid, 2-methoxy-13-methyl-rutaecarpine (**9**), was isolated from the stem bark of an African evergreen tree, *Araliopsis tabouensis*, and exhibited significant antimalarial activity.[15] Indolyl imino methylthioether[16] was converted into amidoxime **7** with hydroxylamine (Scheme 5). Upon simple filtration and evaporation of

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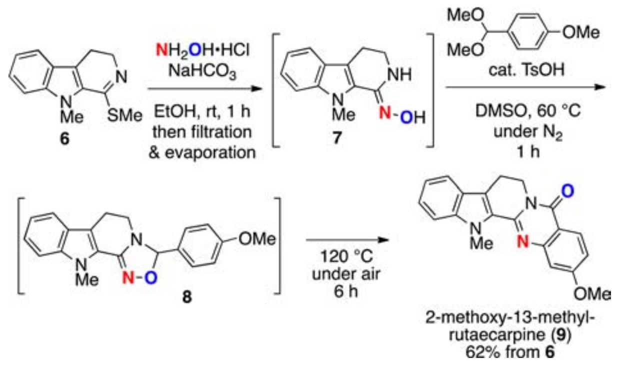
(13) Malacria et al. also observed the formation of the regioisomeric quinazolinone from the substrate bearing a 3-pyridyl group as the iminyl radical acceptor and investigated the possible reaction pathways by theoretical studies; see ref 6c and 6d.

(14) The similar aryl group migration by the reaction of the iminyl moiety was observed; see: (a) Chiba, S.; Zhang, L.; Lee, J.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 7266. (b) McNab, H.; Smith, G. S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 381 and references therein.

(15) Christopher, E.; Bedir, E.; Dunbar, C.; Khan, I. A.; Okunji, C. O.; Schuster, B. M.; Iwu, M. M. *Helv. Chim. Acta* **2003**, *86*, 2914.

(16) Hamid, A.; Elomri, A.; Daïch, A. *Tetrahedron Lett.* **2006**, *47*, 1777.

Scheme 5. A Synthesis of 2-Methoxy-13-methyl-rutaecarpine (**9**)

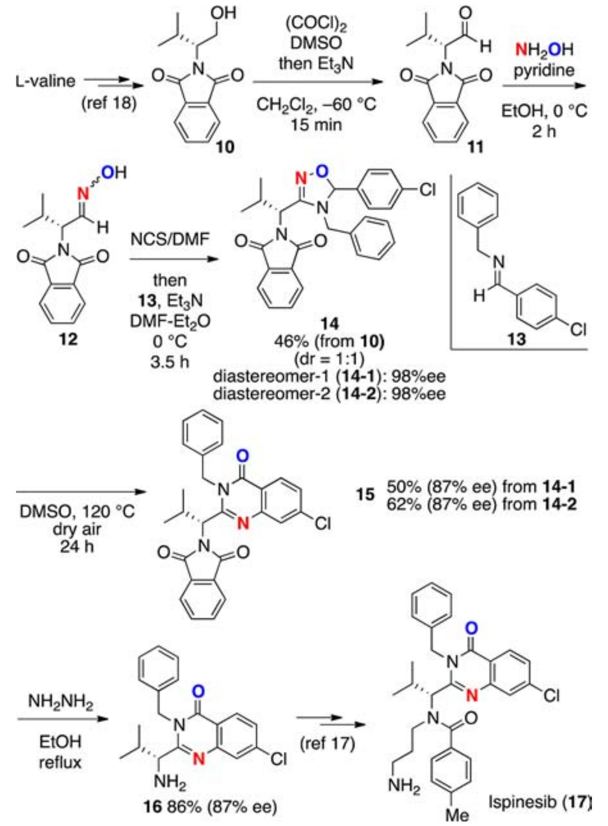


the reaction mixture, the residue including **7** was further treated with 4-anisaldehyde dimethylacetal in the presence of a catalytic amount of TsOH in DMSO to afford dihydro-1,2,4-oxadiazole **8**. Successive aerobic treatment of **8** just by changing the reaction atmosphere to dry air smoothly delivered 2-methoxy-13-methyl-rutaecarpine (**9**) in 62% yield from **6** via simple operations without purification of intermediates **7** and **8**.

Ispinesib (**17**)[17] is an inhibitor of kinesin spindle protein (KSP), which is currently being evaluated under several phase II and I clinical trials for cancer therapies. Optically active alcohol **10** prepared from L-valine[18] was oxidized to α-phthalimidyl aldehyde **11** through Swern oxidation (Scheme 6). Conversion of aldehyde **11** to oxime **12** followed by treatment of **12** with NCS delivered *C*-chlorooxime, which was coupled with aldimine **13** via [3 + 2]-cycloaddition in the presence of Et_3N to afford 4,5-dihydro-1,2,4-oxadiazole **14** as a 1:1 diastereomixture. Aerobic treatment of each isomer of **14** afforded quinazolinone **15** in 62% and 50% yields, in which partial racemization was observed (87% ee each).[19] Further deprotection of the phthalimido moiety of **15** with hydrazine delivered amine **16**, the key precursor of Ispinesib (**17**).

In summary, we have developed an unprecedented oxidative radical skeletal rearrangement of 5-aryl-4,5-dihydro-1,2,4-oxadiazoles induced by molecular oxygen that enables concise assembly of substituted quinazolinones with the simple operation.[20] The present strategy not only serves as an atom- and step-economical alternative to existing synthetic methods but also allows facile construction of quinazolinone cores under tin-free aerobic radical conditions. We are currently engaged in further synthetic applications of this aerobic radical strategy for other types of molecular transformations.

Scheme 6. A Synthesis of Ispinesib Precursor **16**



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Supporting Information Available. Experimental procedures, characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(19) The stereochemistry of each diastereomer **14** was not determined. Interestingly, the aerobic reaction of a mixture of diastereomers **14** was very sluggish, giving **15** in 29% yield (48 h).

(20) A deuterium-labeling experiment suggested that the C−H bond cleavage step is most likely rate-determining for the present quinazolinone formation; see the SI for mode details.