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Radical Annulation of 2-Cyanoaryl Acrylamides via C═C Double Bond Cleavage: Access to Amino-Substituted 2-Quinolones

Wen-Jin Xia, Tai-Gang Fan, Zhi-Wei Zhao, Xin Chen, Xiang-Xiang Wang, and Ya-Min Li*

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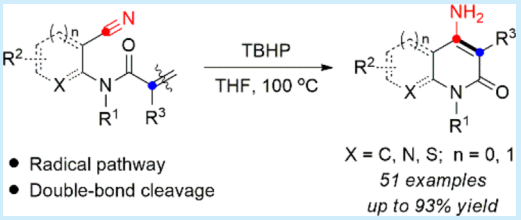
ABSTRACT: A novel annulation of 2-cyanoaryl acrylamides via C═C double bond cleavage has been developed for facile and efficient access to a broad spectrum of functionalized 4-amino-2-quinolones, which are important *N*-heterocycles. In this transformation, the solvent THF is demonstrated to play a crucial role, and the addition of alkyl radicals to nitrile, 1,5-hydride shift, and cleavage of the C−C bond are involved in the mechanism.

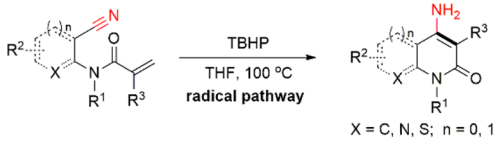


Nitriles are important in organic synthesis due to their versatility in functional group transformations.[1] For example, nitriles can be converted into α-multisubstituted primary amines via nucleophilic addition, which is one of the most common approaches to such compounds. A variety of nucleophiles, most of which are preformed organometallic reagents, such as Grignards, organolithiums, and boranes, have been employed in this transformation.[2] Nitriles are also classical radical acceptors, forming iminyl radicals by the addition of radical species to the cyano group, which can be further transformed into imines.[3] Such radical additions provide great opportunities for the synthesis of ketones, *N*-heterocycles and other C═N double bond moieties;[4] however, the formation of primary amines via radical addition to nitriles has not been well-developed to date.

As a fundamental chemical transformation, the cleavage of C═C double bonds is one of the most efficient tools for furnishing complex molecules that would otherwise be inaccessible by other methods.[5] For instance, ring-closing metathesis (RCM) processes[6] and oxidative cleavage[7] offer facile approaches to various large cyclic hydrocarbons and carbonyl compounds. Recently, the construction of heterocyclic skeletons through radical C═C double bond cleavage have drawn much attention.[8] Rueping and co-workers developed a photoredox catalyzed C═C double bond cleavage reaction of α,β-unsaturated ketones, leading to indole-3-carboxaldehyde derivatives.[8a] Wan, Sheng, and co-workers reported the copper-catalyzed synthesis of 2-aroylbenzothiazoles via cleavage of the enaminone C═C double bond.[8b] Copper-catalyzed alkene aminooxygenation/oxidative carbon−carbon bond cleavage for access to lactams and lactones has also been developed by Wdowik and Chemler.[8c] Yan and his co-workers have also described the formation of C2-substituted indoles, through the simultaneous radical cleavage C═C and C≡C bonds.[8d]

2-Quinolone is an important heterocyclic scaffold which can be found in many natural products, biologically active molecules, and pharmaceuticals[9] and is also a useful synthetic intermediate for the construction of complex molecules.[10] Various synthetic methods for 2-quinolones have been developed,[11−13] and representative approaches include cyclization reactions[11] and the derivatization of quinolones.[12] Despite these advances, most of them suffer from the use of noble metal catalysts, strongly acidic or basic reaction conditions, and limited substrate scope. Thus, developing simple and efficient methods for the production of 2-quinolones still represents a desirable target. As part of our ongoing interest in radical cyclization,[14] we herein report a new radical annulation of 2-cyanoaryl acrylamides via C═C double bond cleavage, for the synthesis of valuable 4-amino-2-quinolones (Scheme 1).

Scheme 1. Annulation of 2-Cyanoaryl Acrylamides



We initially chose *N*-(2-cyanophenyl)-*N*-methylmethacrylamide (**1a**) for establishing an effective reaction system. To our delight, when amine **1a** was subjected to 1.0 equiv of dicumyl peroxide (DCP) in THF at 100 °C for 8 h, the desired amino quinolinone **2a** was obtained in 60% yield (Table 1, entry 1), the structure of which was identified by single-crystal X-ray diffraction analysis. Subsequently, different oxidants including

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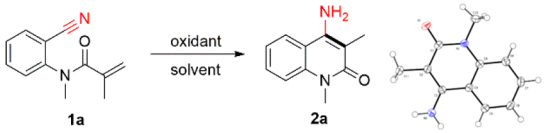
Table 1. Optimization of Reaction Conditions[a]



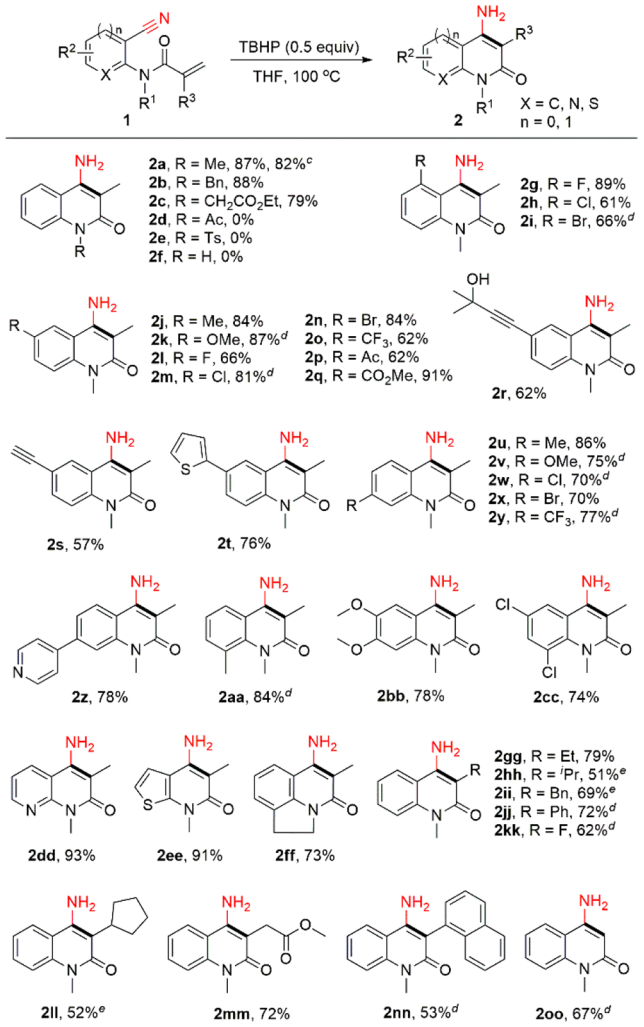
entry	oxidant (equiv)	solvent	time (h)	yield (%)[b]
1	DCP (1)	THF	8	60
2	DTBP (1)	THF	8	53
3	TBPB (1)	THF	8	56
4	TBHP (1)	THF	8	84
5	BPO (1)	THF	8	0
6	$K_2S_2O_8$ (1)	THF	8	0
7		THF	8	0
8	TBHP (2)	THF	8	89
9	TBHP (0.5)	THF	24	87
10	TBHP (0.1)	THF	24	65
11[c]	TBHP (0.5)	THF	24	34
12	TBHP (2)	CH_3CN	8	0
13	TBHP (2)	acetone	8	0
14	TBHP (2)	PhCl	8	0
15	TBHP (2)	hexane	8	0
16	TBHP (2)	dioxane	8	43
17	TBHP (2)	di-*n*-butyl ether	8	39
18	TBHP (2)	tetrahydropyran	8	23

[a]Reaction conditions: **1a** (0.3 mmol) and an oxidant in solvent (2 mL) at 100 °C under air. [b]Isolated yield. [c]Reacted at 70 °C.

di-*tert*-butyl peroxide (DTBP), *tert*-butyl peroxybenzoate (TBPB), *tert*-butyl hydroperoxide (TBHP, 70% aqueous solution), benzoyl peroxide (BPO), and $K_2S_2O_8$ were evaluated; TBHP proved to be the most efficient oxidant, and no product was detected in the absence of any oxidant (Table 1, entries 2−7). The effect of the loading of TBHP was also investigated, and the result indicates that 2.0 equiv of TBHP is optimal, generating product **2a** in 89% yield (Table 1, entry 8). The reaction can also occur in the presence of either substoichiometric or catalytic amounts of TBHP. When **1a** was treated with 0.5 equiv of TBHP for 24 h, product **2a** was obtained in 87% yield (Table 1, entry 9), while reducing the amount of TBHP to 0.1 equiv resulted in an obviously decreased yield of 65% (Table 1, entry 10). When this cyclization was performed at 70 °C, **2a** was obtained in only 34% yield (Table 1, entry 11). It was also found that employing THF as solvent is important for this transformation because no reaction occurred when CH_3CN, acetone, PhCl and hexane were used as solvent (Table 1, entries 12−15). Using other ether solvents such as 1,4-dioxane, di-*n*-butyl ether, and tetrahydropyran resulted in low yields (Table 1, entries 16−18).

With the optimal reaction conditions identified, the substrate scope of this cyclization was investigated (Scheme 2). Different N-protecting groups were initially examined, and the results revealed that 2-cyanoaryl acrylamides with methyl, benzyl, and ester substituents were compatible with this transformation, affording the amino quinolinones **2a**−**2c** in good yields; however, *N*-acetyl, *N*-tosyl, and unprotected N−H substrates were not suitable for the cyclization due to the low reactivity of **1d** and **1f** and for decomposition of **1e**. For the aryl moiety, various aryl acrylamides bearing electron-withdrawing or electron-donating groups on the aryl ring, such as methyl, methoxyl, fluoro, chloro, bromo, trifluoromethyl,

Scheme 2. Substrate Scope[a,b]



[a]Reaction conditions: **1** (0.30 mmol) and TBHP (0.5 equiv) in 2 mL of THF at 100 °C for 24 h. [b]Isolated yield. [c]The reaction was performed in the presence of 7.5 mmol of **1a**. [d]Reaction conditions: **1** (0.30 mmol) and TBHP (2.0 equiv) in 2 mL of THF at 100 °C for 8 h. [e]Reaction conditions: **1** (0.30 mmol) and TBHP (2.0 equiv) in 2 mL of THF at 110 °C for 12 h.

acetyl, and ester groups, were well tolerated with the cyclization (**2g**−**2cc**). Alkynols, alkynes, and heteroarene-substituted phenyl acrylamides also gave the corresponding amino quinolinones in reasonable yields (**2r**, **2s**, **2t**, and **2z**). Heteroaromatic substrates, *N*-pyridinyl and thienyl acrylamides, also reacted smoothly, leading to the corresponding products **2dd** and **2ee** in 93% and 91% yield, respectively. In addition, an indoline derivative was tolerated by the reaction system, and the tricyclic product **2ff** was obtained in 73% yield. The substrate scope with respect to the substituents on the olefin was further examined. Acrylamides with various substituents at the α-position of carbonyl group, such as ethyl, isopropyl, cyclopentyl, ester, benzyl, phenyl, naphthyl, and fluoro, smoothly underwent the cyclization, providing the products **2gg**−**2nn** in moderate to good yields. The substrate with a monosubstituted olefin (R^3 = H) also exhibited high reactivity and 4-amino-quinolinone **2oo** was obtained in 67% yield. When 7.5 mmol of acrylamide **1a** was treated with

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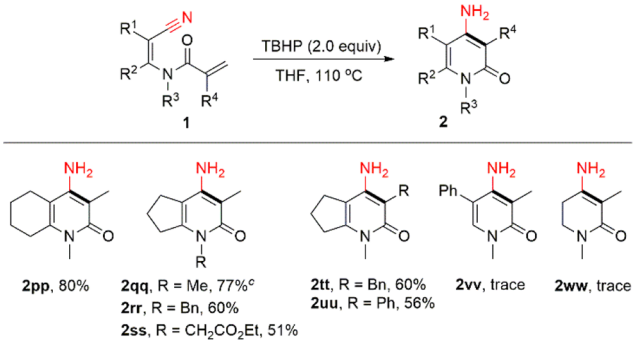
TBHP (2.0 equiv) in THF at 100 °C for 12 h, 4-aminoquinolinone **2a** was obtained in 82% (1.15 g) yield.

It was pleasant to find that 2-cyanovinyl acrylamides are also compatible with this system (Scheme 3), with cyclohexenyl-

Scheme 3. Substrate Scope[a,b]

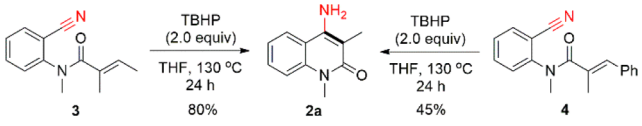


[a]Reaction conditions: **1** (0.30 mmol) and TBHP (2.0 equiv) in 2 mL of THF at 110 °C for 12 h. [b]Isolated yield. [c]Reaction conditions: **1** (0.30 mmol) and TBHP (0.5 equiv) in 2 mL of THF at 100 °C for 24 h.

and cyclopentenyl-substituted acrylamides showing good efficiency, providing the corresponding products **2pp**−**2uu** in reasonable yields. 2-Cyanovinyl acrylamides bearing different groups substituted at the nitrogen atom or the α-position of the carbonyl group, including methyl, benzyl, ester, and phenyl groups, were well tolerated with the cyclization. However, phenyl-substituted 2-cyanovinyl acrylamide was not a suitable substrate for this transformation, and only trace amounts of 4-amino-2-pyridone **2vv** were detected due to the decomposition of substrate. Aliphatic 2-cyanoethyl acrylamide also failed to form the desired product **2ww**.

Subsequently, the annulation of amides bearing an internal alkene was investigated (Scheme 4). When β-methyl-

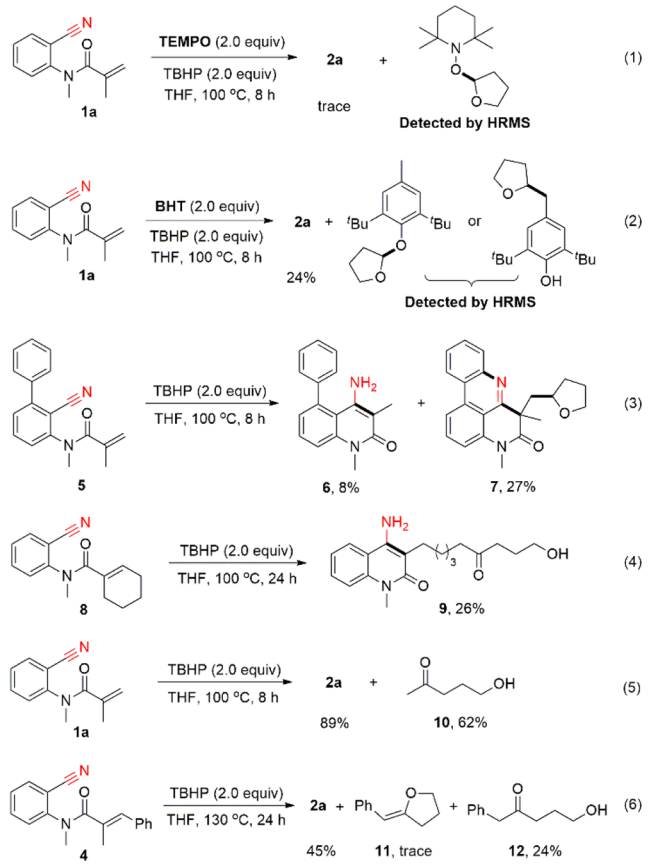
Scheme 4. Cyclization of the Substrates with Internal Olefin



substituted acrylamide **3** served as the substrate, **2a** was isolated in 80% yield. The cleavage of the phenyl-substituted C═C double bond in amide **4** also occurred under this oxidative system, again giving product **2a** in a moderate yield.

To gain insight into the mechanism of this cyclization, a series of mechanistic experiments were performed (Scheme 5). It was found that the cyclization was remarkably inhibited by adding stoichiometric amounts of radical scavengers, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-ditertbutyl-4-methylphenol (BHT), into the reaction system, with both TEMPO-THF and BHT-THF adducts being detected by HRMS [eqs (1) and (2)]. These results reveal that this transformation may proceed via a radical pathway, and THF radical is likely to be involved in the process. Furthermore, when phenyl-substituted 2-cyanoaryl acrylamide **5** was employed as a reactant, quinolinone **6** was obtained in 8% yield, along with 27% yield of a THF moiety-containing *N*-polyheterocycle **7** [eq (3)]. The formation of compound **7** from acrylamide **5** is known, and the mechanism includes an

Scheme 5. Mechanistic Studies



intermolecular addition of a THF radical to the C═C double bond, and two radical-mediated cyclizations, addition of alkyl radical to cyano group and radical substitution of iminyl radical with aromatic ring.[14d] This result suggests that THF is an important participant, and the iminyl radical is a key intermediate in this cyclization.

To further understand the mechanism, the annulation of cyclohexene moiety-containing amide **8** was performed, and the 4-amino-2-quinolinone bearing γ-hydroxyketone **9** was obtained in 26% yield [eq (4)]. In fact, in addition to the quinolinone **2a**, 5-hydroxypentan-2-one **10** was also isolated in the model reaction [eq (6)]. These results indicate that the γ-hydroxyketone is the byproduct of the reaction. Although the byproduct was successfully identified, the detailed mechanism, especially the C═C double bond cleavage step, is still not clear. To our delight, in the reaction of acrylamide **4**, 5-hydroxy-1-phenylpentan-2-one **12** was isolated, and 2-benzylidenetetrahydrofuran **11** was also detected by ^{1}H NMR and HRMS [eq (6)]. It is already known that **12** can be generated by hydrolysis of **11**.[15] Thus, 2-alkenyltetrahydrofuran is probably the leaving fragment after cleavage of C═C double bond.

Based on the above experimental results and previous literature reports,[14,15] a plausible mechanism for this transformation is proposed as depicted in Scheme 6. The *tert*-butoxy radical and hydroxyl radical are initially generated from TBHP through thermal hemolysis. The hydrogen atom abstraction of THF by the *tert*-butoxy or hydroxyl radical then forms THF radical **A**, which undergoes addition to the C═C double bond of acrylamide to provide alkyl radical **B**, followed by an intramolecular cyclization with the nitrile group

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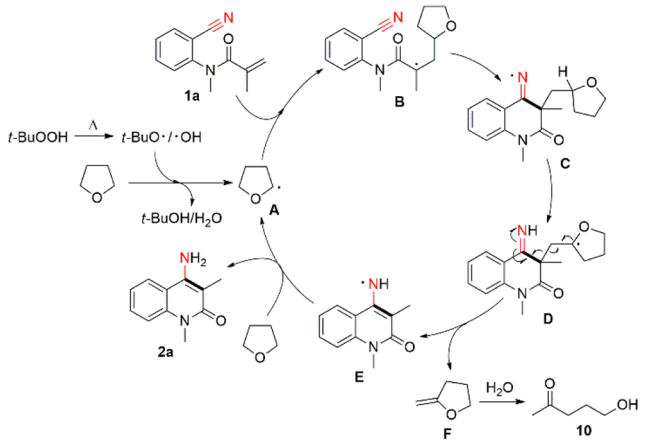
Scheme 6. Proposed Mechanism



to give iminyl radical **C**. Subsequently, intermediate **C** undergoes 1,5-hydrogen atom transfer (HAT) to produce alkyl radical intermediate **D**,[14c] which then undergoes β-cleavage and imine-enamine tautomerism to afford amine radical intermediate **E**, along with 2-alkenyltetrahydrofuran **F**. Finally, H-abstraction by intermediate **E** from THF provides 4-amino-quinolinone **2a** and THF radical **A**. The hydrolysis of 2-alkenyltetrahydrofuran **F** forms γ-hydroxyketone **10**.

In summary, we have developed a novel annulation of 2-cyanoaryl acrylamides via C═C double bond cleavage to construct a wide range of functionalized 4-amino-2-quinolones. This reaction features acid-, base-, and metal-free, simple reaction system, utilization of readily available reagents, and wide substrate scope. The mechanistic study demonstrated that solvent THF is an important participant, and a radical pathway is involved in this transformation. Further application of this reaction are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02281.

Experimental procedures, X-ray crystallography data, charts of compounds, HRMS spectra, and ^{1}H NMR and ^{13}C NMR spectra of compounds (PDF)

Accession Codes

CCDC 2087528 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Ya-Min Li − *Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming 650500, P. R. China;* orcid.org/0000-0003-4233-5274; Email: liym@kust.edu.cn

Authors

Wen-Jin Xia − *Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming 650500, P. R. China*

Tai-Gang Fan − *Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming 650500, P. R. China*

Zhi-Wei Zhao − *Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming 650500, P. R. China*

Xin Chen − *Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming 650500, P. R. China*

Xiang-Xiang Wang − *Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming 650500, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c02281

Notes

The authors declare no competing financial interest.

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