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Tandem Synthesis of Pyrrolo[2,3-*b*]quinolones via Cadogen-Type Reaction

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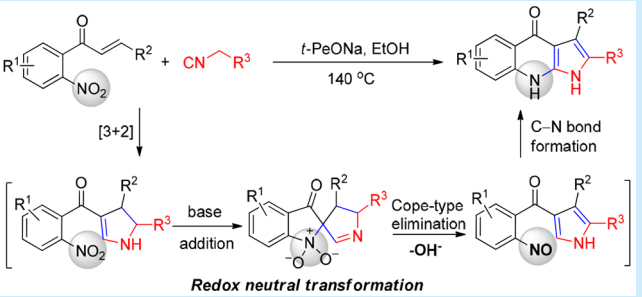
Supporting Information

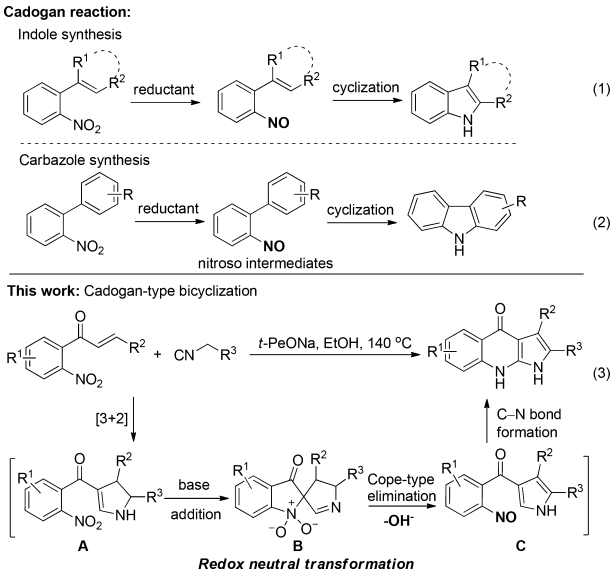
ABSTRACT: A tandem [3 + 2] cycloaddition/reductive cyclization of nitrochalcones with activated methylene isocyanides for the efficient synthesis of pyrrolo[2,3-*b*]-quinolones is reported. In this reaction, the in situ generated dihydropyrroline acts as the internal reductant to convert the nitro into an electrophilic nitroso group, which undergoes subsequent C−N bond formation. Transition-metal-free, simple experimental procedure and ready accessibility of starting materials characterize the present transformation.



Reductive cyclization of *o*-functionalized nitroarenes is one of the most efficient tools for the synthesis of N-containing heterocycles.[1−9] Several named reactions starting from the readily available and cheap nitroarenes, such as Reissert indole synthesis,[2a,b] Leimgruber−Batcho reaction,[2c] Bartoli indole synthesis,[2d,e] and Cadogan reaction,[2f−h] were developed for the preparation of a wide range of aromatic heterocycles. Cadogan reductive cyclization of nitroaromatics using boiling triethyl phosphite is a classic synthetic method for the construction of indoles and carbazoles (Scheme 1, eqs 1 and 2).[2f−h,3] The generally accepted mechanism of Cadogan reaction was suggested by Houk et al., which involves deoxygenation of the nitro group to generate a nitroso intermediate, followed by 6π electrocyclization to form the pyrrole ring.[4] Recent developments on Cadogan-type reaction mainly focus on improvement of its efficiency and practicality, thus superstoichiometric quantities of a reductant such as Grignard reagent,[5] [Mo(CO)$_6$],[6] TiCl$_3$[7] or high pressures of CO[8] were investigated under mild conditions. However, tandem Cadogan-type bicyclization of nitroarenes for the construction of heterocycles remains scarce.[9]

Pyrrolo[2,3-*b*]quinolines are commonly found in pharmacologically active compounds, for example, blebbistatin as myosin II inhibitor,[10] PGP-4008 as P-gp-specific drug release MDR modulator,[11] and some *N*-acyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]-quinoline derivatives used as inhibitors of DU-145 cell proliferation.[12] Since first example of the synthesis of pyrrolo-[2,3-*b*]quinoline derivatives,[13] considerable effort has been devoted to developing new methods for the preparation of these frameworks.[14−19] Generally, previous methods focused on

Scheme 1. Reductive Cyclization of Nitroarenes



stepwise annulations of preformed substituted quinolones[14] or 3-alkylidene-2-(phenylimino)pyrrolidines.[15] Recently, new strategies based on tandem reactions of carbodiimides for one-pot synthesis of these scaffolds were developed.[14−18] In 2010, a facile synthesis of pyrrolo[2,3-*b*]quinolines via a Rh(I)-catalyzed

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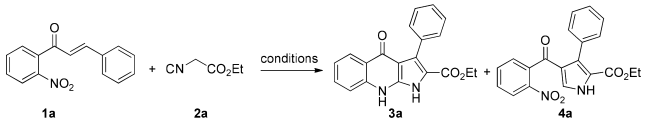
carbodiimide–Pauson–Khand-type reaction was reported.[16] In 2016, an elegant Rh(II)-catalyzed cyclization of azidomethylene-cyclopropanes (MCPs) and isonitriles to afford pyrrolo[2,3-*b*]quinolones was reported.[17] In the same year, I_2/CHP-mediated reaction of amino-MCPs with isonitriles for the synthesis of pyrroloquinolines was developed.[18] An alkoxide-induced rearrangement of 10-membered *N*-acyl cyclic ureas was developed for the synthesis of pyrrolo[2,3-*b*]quinolines.[19] As a result of our studies on the isocyanide-based annulations,[20] we report herein an unprecedented tandem [3 + 2] cycloaddition/Cadogan-type reaction between *ortho*-nitrochalcones and activated methylene isocyanides for the facile and convenient one-pot synthesis of pyrrolo[2,3-*b*]quinolones (Scheme 1, eq 3). In this transformation, the dihydropyrroline moiety of the in situ generated intermediate **A** acts as the reductant to convert the nitro group into reactive nitroso functionality, which facilitates the subsequent C–N bond formation to form the tricyclic framework. Note that, in this reaction, a six-membered pyridone ring is built by forming the C–N bond, whereas in the traditional Cadogen reaction, a five-membered pyrrole ring is generally built.

Initially, the reaction of the nitrochalcone **1a** with ethyl isocyanoacetate **2a** was used as a model reaction to optimize the reaction conditions (Table 1). In the presence of NaOH (1.0 equiv) in ethanol at 140 °C for 2 h, the reaction of **1a** (0.3 mmol) and **2a** (0.6 mmol) gave pyrrolo[2,3-*b*]quinolone **3a**[21] in 52% along with pyrrole **4a** in 21% yield (Table 1, entry 1). It was found that *t*-PeONa (Table 1, entry 4) was the optimal choice after screening different bases such as KOH (Table 1, entry 2), *t*-BuOK (Table 1, entry 3), *t*-PeONa (Table 1, entry 4), Cs_2CO_3 (Table 1, entry 5), and DBU (Table 1, entry 6). The reaction gave slightly lower yield of **3a** either decreasing the amount of *t*-PeONa to 0.5 equiv (Table 1, entry 7) or increasing the amount to 2.0 equiv (Table 1, entry 8). Selected solvents, such as MeOH, *i*-PrOH, *t*-BuOH, CH_3CN, toluene, DCE, and 1,4-dioxane, were examined but gave **3a** in lower yields (Table 1, entries 9–15). When the reaction temperature was increased to 150 °C, **3a** was obtained in 50% yield (Table 1, entry 16), whereas upon decreasing the temperature to 120 °C, the yield of **3a** was much lower (Table 1, entry 17). When the reaction was performed under more diluted conditions (Table 1, entries 18–20), the yield of **3a** was increased to 73% (concentration = 0.03 M, Table 1, entry 19).

Table 1. Optimization of the Reaction Conditions[a]

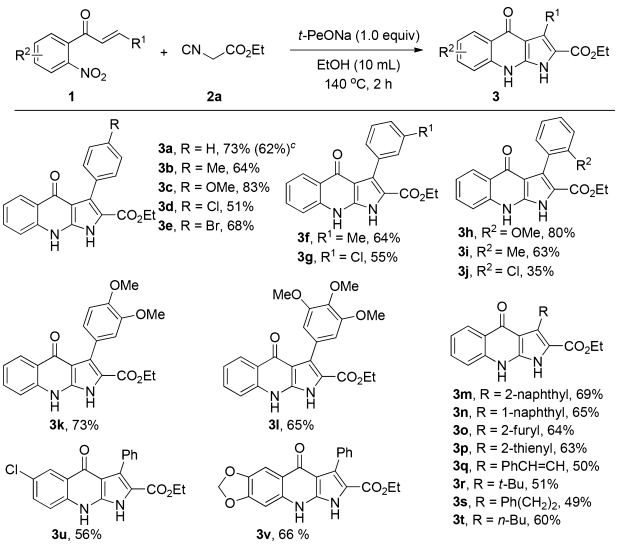


entry	base (1.0 equiv)	solvent	temp (°C)	yield (%)[b] 3a	4a
1	NaOH	EtOH	140	52	21
2	KOH	EtOH	140	40	31
3	*t*-BuOK	EtOH	140	41	37
4	*t*-PeONa	EtOH	140	56	29
5	Cs_2CO_3	EtOH	140	17	45
6	DBU	EtOH	140	40	11
7[c]	*t*-PeONa	EtOH	140	40	33
8[d]	*t*-PeONa	EtOH	140	51	21
9	*t*-PeONa	MeOH	140	55	27
10	*t*-PeONa	*i*-PrOH	140	47	26
11	*t*-PeONa	*t*-BuOH	140	33	11
12	*t*-PeONa	CH_3CN	140		trace
13	*t*-PeONa	toluene	140	trace	
14	*t*-PeONa	DCE	140	trace	
15	*t*-PeONa	dioxane	140	trace	
16	*t*-PeONa	EtOH	150	50	29
17	*t*-PeONa	EtOH	120	44	23
18[e]	*t*-PeONa	EtOH	140	63	26
19[f]	*t*-PeONa	EtOH	140	73	22
20[g]	*t*-PeONa	EtOH	140	72	21

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), base (0.3 mmol), solvent (2 mL), air atmosphere, 2 h. [b]Yield of isolated products. [c]*t*-PeONa (0.5 equiv) was added. [d]*t*-PeONa (2.0 equiv) was added. [e]EtOH (5 mL). [f]EtOH (10 mL). [g]EtOH (15 mL).

With the optimal conditions in hand (Table 1, entry 19), the scope of viable **1** was examined; the results are summarized in Scheme 2. A wide range of substrates **1** were tolerated in this reaction, and a series of pyrrolo[2,3-*b*]quinolones (**3a–v**) were produced in good to high yields by the reactions of **2a** with a wide range of **1** bearing various R^1 groups, e.g., *para*- (**1b–e**), *meta*- (**1f,g**), and *ortho*-substituted aryl groups (**1h–j**), disubstituted phenyl groups (**1k**), trisubstituted phenyl groups (**1l**), 1- and 2-naphthyl (**1m,n**), heteroaryl groups (**1o,p**), vinyl group (**1q**), and alkyl groups (**1r–t**). This reaction also tolerated **1** bearing both electron-withdrawing (**1u**) and -donating R^2 groups (**1v**).

Scheme 2. Scope of Nitrochalcones 1[a,b]



[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.6 mmol) and *t*-PeONa (1.0 equiv) in EtOH (10 mL) at 140 °C. [b]Isolated yields. [c]1 mmol scale.

Subsequently, the scope of the reaction was evaluated with respect to activated methylene isocyanides **2** (Scheme 3). Under the optimal conditions (Table 1, entry 19), methyl isocyanoacetate **2b**, *tert*-butyl isocyanoacetate **2c**, and isocyanoacetamide **2d** gave the corresponding pyrrolo[2,3-*b*]quinolones **3w–y** in moderate yields. Furthermore, the reaction also tolerated substituted benzyl isocyanides **2f** and **2g** and gave the 2-aryl-substituted pyrrolo[2,3-*b*]quinolones **3z–3aa** in moderate yields. Reaction of **1a** with tosylmethyl isocyanide **2e** gave pyrrole product **5a** with the nitro groups intact, and the corresponding pyrrolo[2,3-*b*]quinolone **3ab** was not detected.

Control experiments were performed to clarify the reaction mechanism. In the presence of Ag_2CO_3 (0.3 equiv), the reaction

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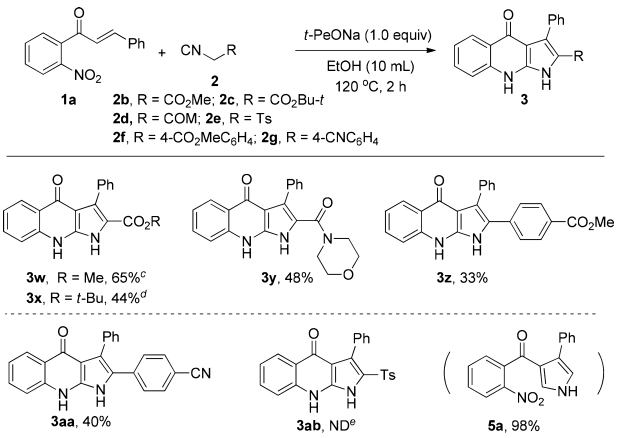
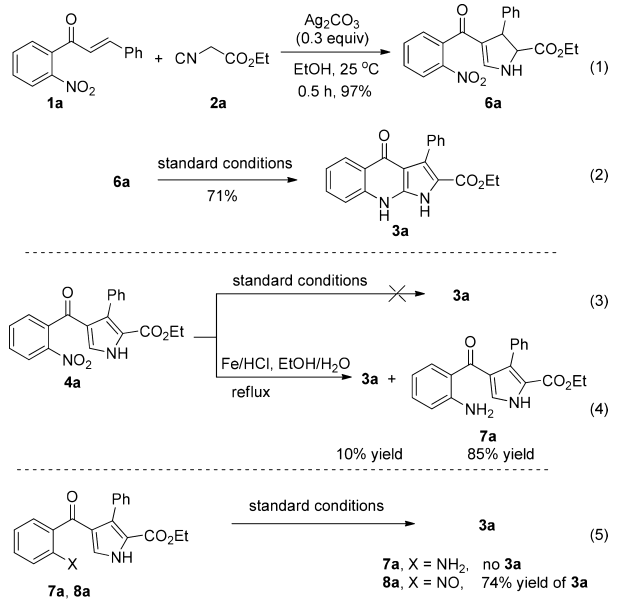
Scheme 3. Scope of Activated Methylene Isocyanides 2[a,b]



[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.6 mmol) and *t*-PeONa (1.0 equiv) in EtOH (10 mL) at 140 °C. [b]Isolated yields. [c]MeOH as solvent. [d]*t*-BuOH as solvent. [e]ND = not detected.

of **1a** with **2a** took place easily at room temperature within 0.5 h to give dihydropyrroline **6a** in 97% yield (Scheme 4, eq 1). **6a** was

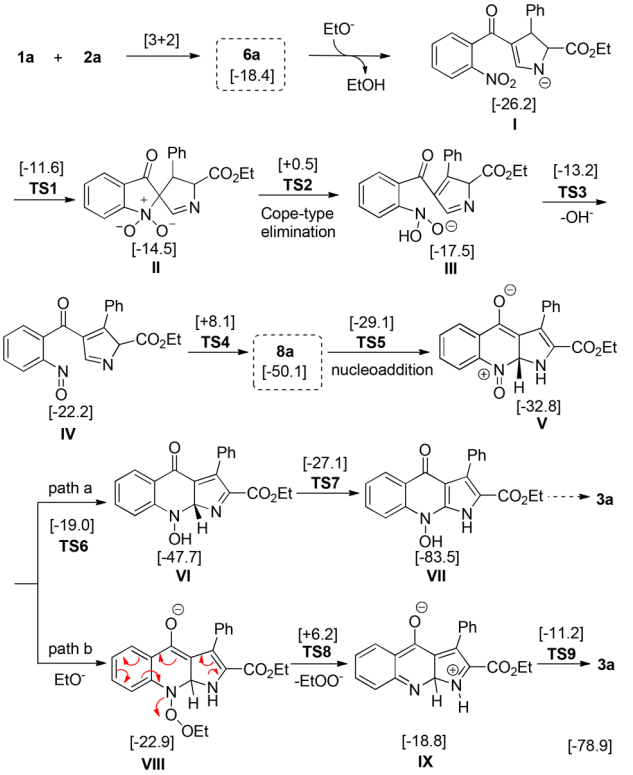
Scheme 4. Control Experiments



converted to **3a** in 71% yield under the standard conditions (Scheme 4, eq 2). These results show that **6a** is probably the intermediate in this tandem [3 + 2] cycloaddition/C−N bond formation reaction. When *ortho*-nitrobenzoylpyrrole **4a** was treated with the standard conditions, **3a** was not detected (Scheme 4, eq 3). However, **3a** was obtained in 10% yield when **4a** was reduced with Fe/HCl (Scheme 4, eq 4). Furthermore, when *ortho*-aminobenzoylpyrrole **7a** was treated with the standard conditions, **3a** was not detected either, in contrast, **3a** was obtained in 74% yield from the reaction of *ortho*-nitrosobenzoylpyrrole **8a** under the standard conditions (Scheme 4, eq 5). These results suggested that **8a** was most likely an intermediate on the way to **3a**.

Transformation of **6a** to **8a** is a redox-neutral process, in which the dihydropyrroline moiety of **6a** acts as the internal reductant to convert the nitro group into reactive nitroso functionality. To gain further insight into this interesting redox-neutral transformation, DFT calculations were carried out at the B3LYP level (see Supporting Information). As shown in Scheme 5, the

Scheme 5. Plausible Reaction Pathways



enthalpy profile indicates that the reaction initiating from **1a** and **2a** proceeds through [3 + 2] cycloaddition to form **6a**.[20c,d,22] Deprotonation of **6a** takes place to form anion **I**, then intramolecular cyclization of intermediate **I** produces the spiro intermediate **II**[9,23] via **TS1** (TS = transition state) with an activation barrier of 14.6 kcal/mol. Cope-type elimination[24] of **II** by way of **TS2** forms anion **III**, which undergoes successive dehydroxylation and proton shift to form the reactive **8a** via transition states **TS3** and **TS4**, with activation barriers of 4.3 and 30.3 kcal/mol, respectively. Nucleoaddition of nitroso to pyrrole[5] furnishes intermediate **V** with an activation barrier of 21 kcal/mol. It is most likely that two possible paths exist on the way from **V** to **3a**. In path a, a hydride shift from N to O atom occurs to give intermediate **VI** with an activation barrier of 13.8 kcal/mol, following by proton shift to generate *N*-hydroxy pyrroloquinolone **VII** via **TS7** with an activation barrier of 20.6 kcal/mol. The cleavage of the N−O bond of **VII** may provide the final product **3a**.[4,7] In path b, nucleoaddition of an ethoxy anion to **V** results in intermediate **VIII**, which is followed by the elimination of $EtOO^-$ to furnish **IX** via **TS8** with an activation barrier of 29.1 kcal/mol.[9] Finally, proton shift of intermediate **IX** leads to **3a** via **TS9** with an activation barrier of 7.6 kcal/mol. At this stage, the evidence for the reductive cleavage of the N−O bond of **VII** seems absent, thus path b may be the preferred way.

To demonstrate the synthetic potential of this bicyclization reaction, transformations of the generated pyrroloquinolone **3** were conducted (Scheme 6). **3a** was readily converted to 4-chloropyrrolo[2,3-*b*]quinoline **9** by chlorination with $POCl_3$ in high yield. Substitution of the chloro group with primary amines

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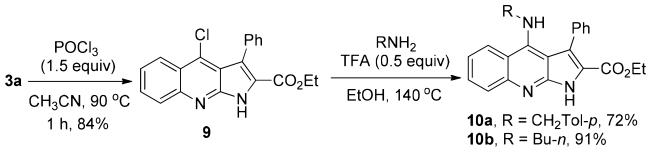
Scheme 6. Potential Synthetic Applications of 3



furnished the 4-aminopyrrolo[2,3-*b*]quinoline **10a,b** in good to excellent yields.

In summary, a tandem [3 + 2] cycloaddition/reductive cyclization of nitrochalcones with activated methylene isocyanides was developed for the efficient and practical synthesis of pyrrolo[2,3-*b*]quinolones. Control experiments showed that the in situ formed dihydropyrroline acting as the internal reductant converts the nitro into a reactive nitroso group, which rendered the subsequent C−N bond formation. Transition-metal-free, simple experimental procedure, ready accessibility of the starting materials, and good to high yields characterize the present transformation. The investigation of tandem Cadogen-type cyclization of nitroarenes is ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02558.

Experimental procedures and characterization data for all compounds (PDF)
X-ray data of **3a′** (CIF)

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Notes

The authors declare no competing financial interest.

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(21) CCDC 1558765 (**3a′**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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