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Expeditious Synthesis of Multisubstituted Quinolinone Derivatives Based on Ring Recombination Strategy

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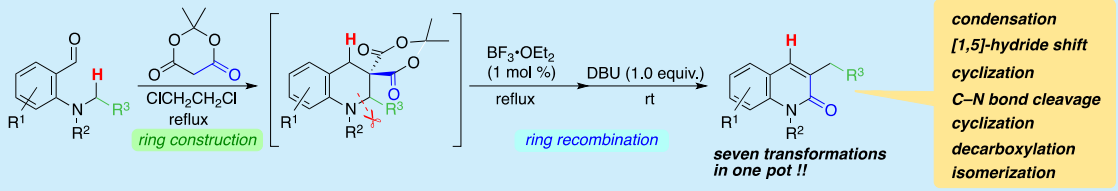
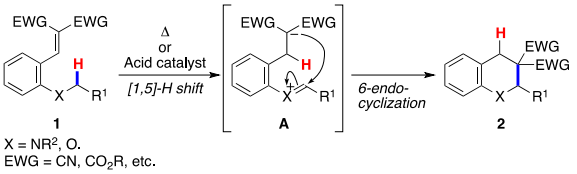
Supporting Information



ABSTRACT: We achieved a concise construction of 3-substituted quinolinone derivatives based on a ring recombination strategy. In this process, seven transformations involving two types of cyclization proceeded in one pot to afford various quinolinone derivatives in good to excellent chemical yields (up to 98%).

Carbon−hydrogen bond functionalization is a powerful tool in modern synthetic organic chemistry. Because of its utility from the perspectives of atom economy and step economy, many organic chemists have devoted time and effort to the development of novel reactions.[1] Recently, we have also been interested in the development of a novel C−H bond functionalization reaction via an intramolecular hydride shift/cyclization process, as described in Scheme 1.[2−7] This reaction

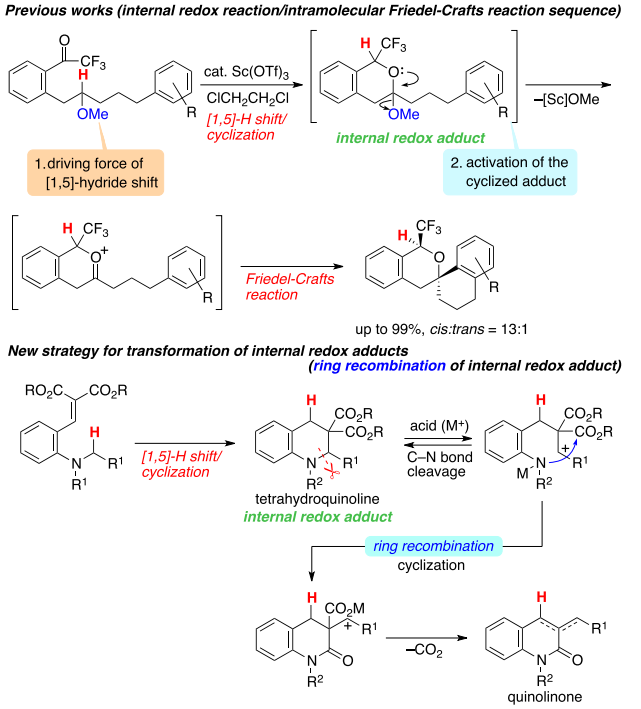
Scheme 1. C(sp^3)−H bond Functionalization by Hydride Shift/Cyclization Process (Internal Redox Process)



system has four features: (1) functionalization of an inert C(sp^3)−H bond, (2) without use of external oxidants (reducing the amount of wastes), (3) simple Lewis and/or Brønsted acids catalyzed reaction (without transition metal catalyst), and (4) construction of a polycyclic framework. The last point (point 4) is worth emphasizing. Various useful heterocycles, such as tetrahydroquinolines,[6] tetrahydroisoquinolines,[3e,g,6u] quinazolines,[3a,7e] tetralins,[3c,d,h,7m] and indoles,[3l] could be elegantly constructed.

Although this reaction system has high synthetic potential, it has a major drawback as well: narrowness of the synthetic transformation from the cyclized adduct (internal redox adduct). In this context, we recently reported an effective strategy, as shown in the upper part of Scheme 2. The key point is the dual role of the heteroatom as (1) a driving force of the hydride shift and (2) an activator of the resulting

Scheme 2. Two Strategies for Further Transformation from the Internal Redox Adduct



cyclized adduct by acting as a leaving group, which enables the highly diastereoselective synthesis of CF_3-substituted spiroisochromans.[3m]

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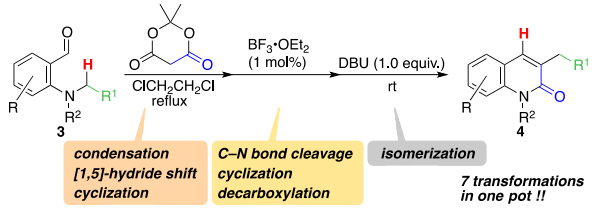
Org. Lett. XXXX, XXX, XXX−XXX

As an alternative strategy for achieving the goal, we focused on the ring recombination of the cyclized adduct. The strategy is described in the lower part of Scheme 2. Tetrahydroquinolines are selected as the suitable internal redox adduct due to the presence of a relatively labile C−N bond at β-position to the dicarbonyl moiety. We envisioned that if the target C−N bond could be cleaved under an acid catalyst and a subsequent cyclization reaction of the resulting aniline moiety and ester portion occurred, another useful skeleton, quinolinone derivatives, would be obtained. There are two challenges, however: (1) the selective cleavage of the targeted C−N bond and (2) preferential bond formation between the resulting amine portion and ester portion over bond reformation.

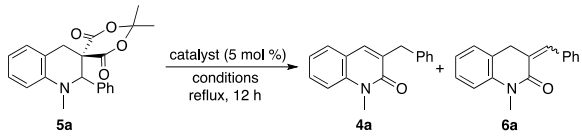
Herein we wish to report the realization of this concept. The reaction consists of seven transformations (condensation/hydride shift/cyclization/C−N bond cleavage/cyclization/decarboxylation/isomerization). Subjecting a mixture of aldehyde **3** and Meldrum's acid to neutral conditions (simple heating), acidic conditions (1 mol % of $BF_3{\cdot}OEt_2$), and basic conditions (1.0 equiv of DBU) in succession in the same reaction vessel enabled the above-described seven transformations to afford various quinolinone derivatives **4** in good to excellent chemical yields (Scheme 3).

Scheme 3. One-Pot Synthesis of Quinolinone Derivatives via Internal Redox Reaction/Ring Recombination/Isomerization Sequence



Details of the screening for the reaction conditions are listed in Table 1. We envisioned tetrahydroquinoline derivative **5a** with Meldrum's acid moiety as the suitable substrate because of its high susceptibility to nucleophilic attack of Meldrum's acid. At the outset, a solution of **5a** in $ClCH_2CH_2Cl$ was treated with 5 mol % of $Sc(OTf)_3$, which worked as an effective catalyst in most of the internal redox reactions we had developed.[3] Gratifyingly, the desired ring recombination process proceeded to give desired **4a** in 12% chemical yield (entry 1). In this case, two structural isomers (*E*)- and (*Z*)-**6a** with an *exo*-double bond were obtained as the major product (80% chemical yield) and their *E*/*Z* ratio was 24/76. Because **4a** and **6a** could not be separated by silica gel column chromatography, their chemical yields were determined by ^1H NMR measurement. Examination of the acid catalysts indicated that most of the acid catalysts were effective for the desired process, although the ratios of **4a** to **6a** were slightly different (entries 2−11). Various metal triflates, such as $Yb(OTf)_3$, $Gd(OTf)_3$, $Sn(OTf)_2$, and $Zn(OTf)_2$, afforded adducts **4a** and **6a** in good to excellent chemical yields (78−98% combined chemical yields, entries 2−6). Excellent conversion was also observed with commonly used strong Lewis acids ($TiCl_4$, $SnCl_4$, $BF_3{\cdot}OEt_2$, entries 7−9) and Brønsted acids (TfOH and Tf_2NH, entries 10 and 11). Based on the above results, we set $BF_3{\cdot}OEt_2$ as the optimal acid catalyst because of low cost and ease of handling, and conducted a more detailed screening for the reaction conditions (entries 12−17). Gratifyingly, the catalyst loading could be reduced to 1 mol % without sacrificing chemical yields (89%, entry 13). Examination of reaction solvents suggested that most of the solvents could be employed in this reaction, with $ClCH_2CH_2Cl$ being the best. As expected, the high reactivity of Meldrum's acid moiety was important to promote the desired reaction: a less reactive substrate with a dimethyl malonate moiety did not afford the desired quinolinone derivative, and complete recovery of starting material was observed (entry 18).

Table 1. Examination of Reaction Conditions[a]



entry	catalyst	yield (%)[b] 4a	6a (*E*/*Z*)	5a
1	$Sc(OTf)_3$	12	80 (24/76)	–
2	$Yb(OTf)_3$	13	85 (19/81)	–
3	$Gd(OTf)_3$	9	74 (14/86)	–
4	$Mg(OTf)_2$	–	–	99
5	$Sn(OTf)_2$	33	45 (0/100)	–
6	$Zn(OTf)_2$	34	48 (0/100)	–
7	$TiCl_4$	29	66 (38/62)	–
8	$SnCl_4$	21	51 (41/59)	–
9	$BF_3{\cdot}OEt_2$	7	86 (17/83)	–
10	TfOH	27	56 (34/66)	12
11	Tf_2NH	23	55 (38/62)	20
12[c]	$BF_3{\cdot}OEt_2$	10	88 (28/72)	–
13[d]	$BF_3{\cdot}OEt_2$	10	89 (28/72)	–
14[d,e]	$BF_3{\cdot}OEt_2$	10	77 (34/66)	–
15[d,f]	$BF_3{\cdot}OEt_2$	17	73 (21/79)	–
16[d,g]	$BF_3{\cdot}OEt_2$	26	63 (41/59)	–
17[d,h]	$BF_3{\cdot}OEt_2$	24	–	95
18[d,i]	$BF_3{\cdot}OEt_2$	24	–	95

[a]Unless otherwise noted, all reactions were conducted with 0.10 mmol of **5a** in the presence of 5 mol % of catalyst in $ClCH_2CH_2Cl$ (1.0 mL) at refluxing temperature. [b]Isolated yield. [c]3 mol % of acid catalyst. [d]1 mol % of acid catalyst. [e]In benzene. [f]In toluene. [g]In xylene. [h]In CH_2Cl_2. [i]Dimethyl malonate derivative was used as the starting material.

Thus, we were able to develop an effective catalytic transformation from the internal redox adduct. However, one problem remained unsolved. Compounds **4a** and **6a** were obtained as an inseparable mixture in all cases, which is the major drawback of the present method for practical use. Nevertheless, we were pleased to find that treatment of the mixture of **4a** and **6a** in CH_3CN with a stoichiometric amount of DBU (1.0 equiv) induced the complete double-bond isomerization in **6a** to afford quinolinone **4a** in excellent chemical yield (95%).[8] Importantly, this isomerization reaction could also be conducted in $ClCH_2CH_2Cl$ without sacrificing the chemical yield (91%). Furthermore, not only the condensation of aldehyde **3a** and Meldrum's acid but also the [1,5]-hydride shift/cyclization process proceeded smoothly by only heating a mixture of them in $ClCH_2CH_2Cl$. The smooth progress of the three reactions [(1) **3a** to **5a**, (2) **5a** to **4a** and **6a**, and (3) a mixture of **4a** and **6a** to **4a**] in the same solvent system provided motivation to conduct a one-pot reaction. Refluxing a mixture of **3a** and Meldrum's acid in

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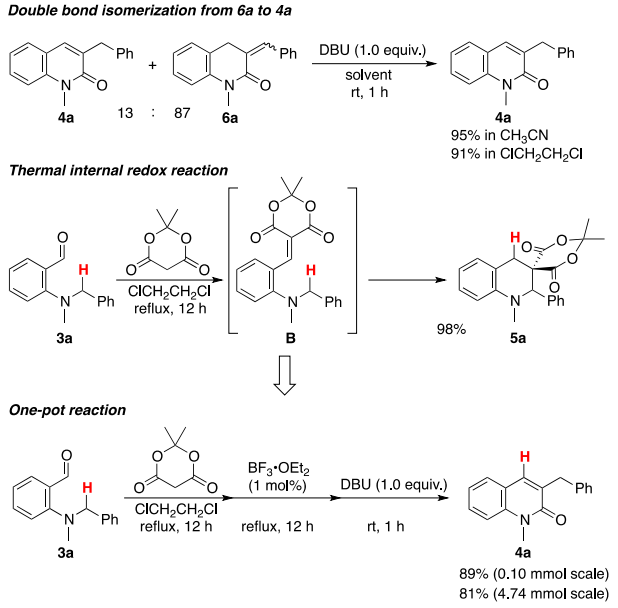
Org. Lett. XXXX, XXX, XXX−XXX

$ClCH_2CH_2Cl$ for 12 h and additional reflux for 12 h after the addition of 1 mol % of $BF_3{\cdot}OEt_2$ followed by 1 h of stirring at room temperature in the presence of DBU afforded quinolinone **4a** in excellent chemical yield (89%). Importantly, this one-pot reaction could be conducted in 4.74 mmol scale (81%), which clearly indicates the high practicability of the present method (Scheme 4).

Scheme 4. Toward a One-Pot Reaction



With the optimized one-pot protocol, the substrate scope of this quinolinone synthesis was examined (Figure 1). Initially, the substituent effect on the nitrogen atom was surveyed, which suggested that employment of a benzyl group was important to achieve good chemical yields. Substrates **3a**–**e** possessing various types of benzyl group participated in the reaction, and corresponding adducts **4a**–**e** were obtained in good to excellent chemical yields (82–90%). *N*,*N*-Dibenzylamine derivative **3f** also afforded desired adduct **4f** in excellent chemical yield (89%). On the other hand, the chemical yield of product **4g** decreased to only 29% when *N*,*N*-diethylamine substrate **3g** was employed.

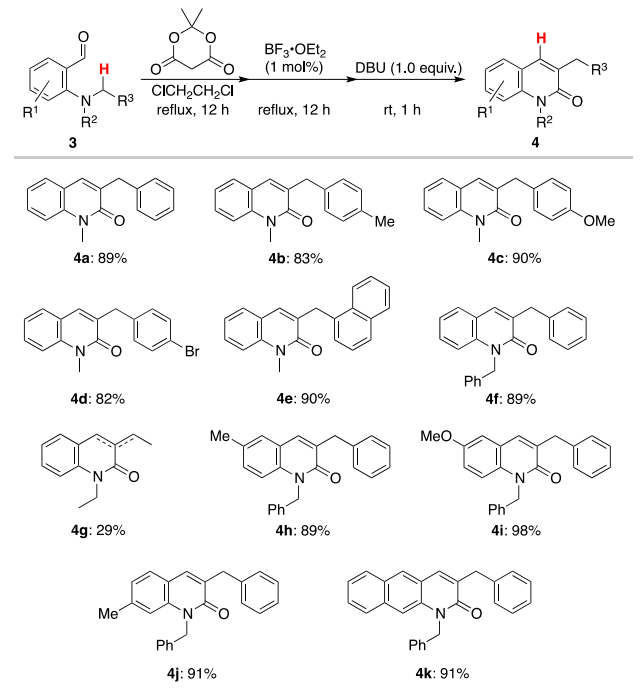


Figure 1. Substrate scope.

In sharp contrast to the limitation of the substituents on the amine moiety, the substituent on the mother aromatic ring (R^1) was almost negligible (an amine group was fixed to the *N*,*N*-dibenzyl amine group because of its easy preparation). Various quinolinone derivatives **4h**–**j** and tricyclic analogue **4k** were obtained in good to excellent chemical yields (89–98%).

There are two possible pathways for the formation of **4**/**6** from **5** (Figure 2). One possible pathway (path I) is the proposed mechanism described in Scheme 2, in which acid-promoted C–N bond cleavage is involved as the key step. Subsequent intamolecular cyclization followed by decarboxylation affords **4**/**6**. Ring opening initiated by the nucleophilic addition of a nucleophile (H_2O is most likely) followed by the intramolecular amide formation (cyclization) is another possible pathway (path II).

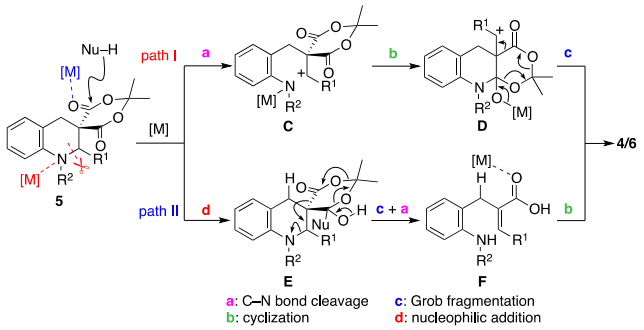


Figure 2. Two possible pathways for the formation of **4**/**6** from **5**.

Additional experiments imply that path I would be a more reliable pathway (Figure 3). Heating **5a** in water-containing reaction medium (H_2O–dioxane system) in the absence of $BF_3{\cdot}OEt_2$ gave not quinolinone **4a**/**6a** but simple lactam **7**[9] in moderate chemical yield (55%, eq 1). In addition, the reaction in the presence of a dehydrating agent (MS5 Å) resulted in

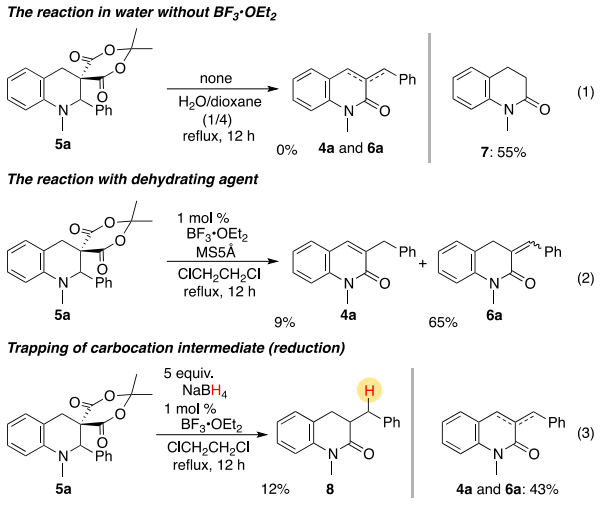


Figure 3. Additional experiments for clarifying reaction mechanisms.

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Org. Lett. XXXX, XXX, XXX–XXX

almost the same level of conversion as the optimized reaction conditions (74%, eq 2. cf. 99%, entry 13 in Table 1). These results would rule out the nucleophilic addition initiated reaction pathway. The possibility of the C−N bond cleavage pathway was further supported by a cation-trapping experiment (eq 3). When a solution of **5a** was treated with 1.0 mol % of BF_3·OEt_2 and 5 equiv of $NaBH_4$, saturated product **8** was obtained in 12% chemical yield, accompanied by normal products **4a** and **6a** (43%).[10]

In summary, we have developed an effective synthetic method to generate multisubstituted quinolinone derivatives via a C−N bond cleavage induced ring recombination strategy. This method has two features: (1) accomplishment of seven transformations including C(sp^3)−H bond functionalization and C−N bond cleavage in one pot, and (2) a simple reaction procedure (only mixing the substrate, acid, and base). Additional experiments suggested that the proposed acid-promoted C−N bond cleavage mechanism would be the most reliable pathway. Further investigation of the synthesis of more complex cyclic structures starting from internal redox adducts is underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04224.

Experimental procedures, analytical and spectroscopic data for new compounds, copies of NMR spectra, computational details, and Cartesian coordinates (PDF)

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Notes

The authors declare no competing financial interest.

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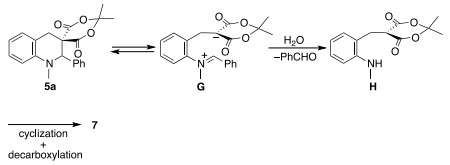
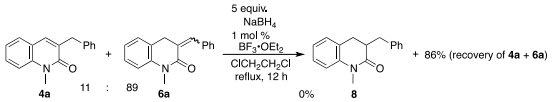
(9) The formation of **7** was ascribed to ring opening to produce zwitterionic intermediate **G**, hydrolysis to aniline moiety **H**, and finally cyclization and decarboxylation.



(10) Treatment of a mixture of **4a** and **6a** (**4a**/**6a** = 11/89) with 1 mol % $BF_3{\cdot}OEt_2$ and 5 equiv of $NaBH_4$ resulted in the recovery of SMs (**4a** and **6a**: 86%), which clearly indicates that saturated compound **8** was produced by trapping the carbocation intermediate.



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