Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

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Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Base-promoted annulation of *α*-hydroxy ketones and dimethyl but-2-ynedioate : straightforward access to pyrano[4,3-*a*]quinolizine-1,4,6(2*H*)-triones and 2*H*-pyran-2,5(6*H*)-diones*

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

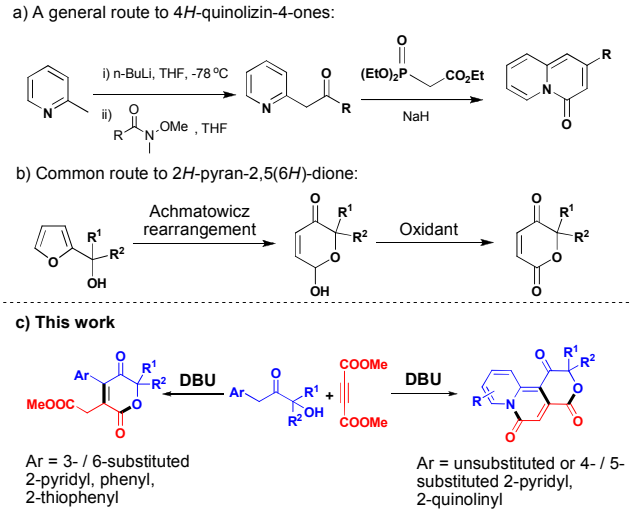
DOI: 10.1039/b000000x

A novel and efficient cascade annulation of tertiary *α*-hydroxy ketones and dimethyl but-2-ynedioate is reported. The reaction, which only requires a base as the promoter, provides a straightforward access to polysubstituted pyrano[4,3-*a*]quinolizine-1,4,6(2*H*)-triones and 2*H*-pyran-2,5(6*H*)-diones under very mild reaction conditions.

Heterocyclic compounds are widely found in nature occurring products and designed compounds with important biological and pharmaceutical properties.[1] Therefore, the development of improved methodologies for the rapid construction of heterocycles remains one of the most attractive and challenging goal for the synthetic organic chemists.[2]

4*H*-quinolizin-4-ones constitute an important class of biologically active heterocycles and exhibit a range of physiological activities including antibacterial and antimicrobial activities.[3] Their derivatives have also found a new use in the design of novel magnesium fluorescent probe.[4] However, approaches for the construction of 4*H*-quinolizin-4-one motifs are very scarce.[5] Until recently, Watson and co-workers reported a general method to synthesize 2-substituted 4*H*-quinolizin-4-ones by using a two-step reaction sequence (Scheme 1, a).[5e] On the other hand, 2*H*-pyran-2,5(6*H*)-dione derivatives are versatile intermediates in organic synthesis,[6] as illustrated by the concise syntheses of many bioactive natural products, including ipomoeassin B and E,[6b] basiliolide B,[6d] and (-)-rasfonin.[6e] Surprisingly, and to the best of our knowledge, only one approach is available for the synthesis of 2*H*-pyran-2,5(6*H*)-diones, consisting of an Achmatowicz rearrangement reaction of furan-2-yl carbinols and a subsequent oxidation reaction (Scheme 1, b).[6,7] Moreover, the fused-ring compounds of 4*H*-quinolizin-4-one and 2*H*-pyran-2,5(6*H*)-dione motifs, pyrano[4,3-*a*]quinolizine-1,4,6(2*H*)-triones, have not been developed with regard to their synthesis and biological activity so far. Therefore, the development of novel and versatile methods to construct these useful heterocyclic compounds is highly desirable, which can undoubtedly stimulate their biological studies and help drug discovery.

Recently, we have developed a green method for the efficient synthesis of tertiary α-hydroxy ketones through CO_2-promoted and silver-catalyzed regioselective hydration of propargylic alcohols.[8] In order to further explore the utility of the method in organic synthesis, combined with our continuous effort in the development of efficient methods for the construction of heterocyclic compounds from alkynoates,[9] herein, we hope to present a base-promoted annulation reaction between tertiary *α*-hydroxy ketones and dimethyl but-2-ynedioate for straightforward synthesis of pyrano[4,3-*a*]quinolizine-1,4,6(2*H*)-triones and 2*H*-pyran-2,5(6*H*)-diones under very mild reaction conditions.

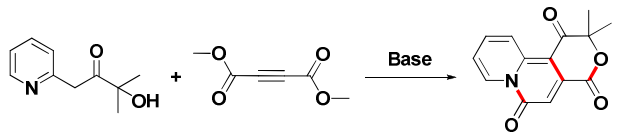


Scheme 1 Synthetic strategies to 4*H*-quinolizin-4-ones and 2*H*-pyran-2,5(6*H*)-diones.

We began our studies with the model reaction of 3-hydroxy-3-methyl-1-(pyridin-2-yl)butan-2-one (**1a**) and dimethyl but-2-ynedioate (**2**). To our surprise, just by simple mixing of **1a** and **2** in DMF in the presence of DBU (1,8-diazabicyclo[5.4.0]-undec-7-ene) at 50 °C under stirring condition for 1 h, an unexpected tricyclic compound, 2,2-dimethylpyrano[4,3-a]quinolizine-1,4,6(2*H*)-trione (**3a**), was obtained in excellent yield (Table 1, entry 1). It is very interesting because in this transformation, three different bonds, C-C, C-O, and C-N bond were formed in one step in the absence of any metal catalyst. Further screening of the base showed that other bases, such as 4-(*N*,*N*-dimethylamino)pyridine (DMAP), 1,4-Diazabicyclo[2.2.2]octane

(DABCO), Na_2CO_3 and NaOH can also work well to furnish the desired product in good yields (Table 1, entries 2, 3, 5 and 6). However, the yields of the product were dramatically decreased when *N*,*N*-diisopropylethylamine (DIPEA) was employed for the reaction. Notably, the reaction could take place in room temperature while the yield of **3a** remained unchanged (Table 1, entry 7). The optimization of the loading of the base showed that even when the loading of DBU was decreased to 25 mol %, the reaction proceeded smoothly to give the desired product in 85% yield (Table 1, Entry 8). Solvent screening revealed that DMSO and acetonitrile were also good solvents for the transformation while methanol gave an inferior result (Table 1, entries 9-11).

Table 1 Optimization of reaction conditions[a]



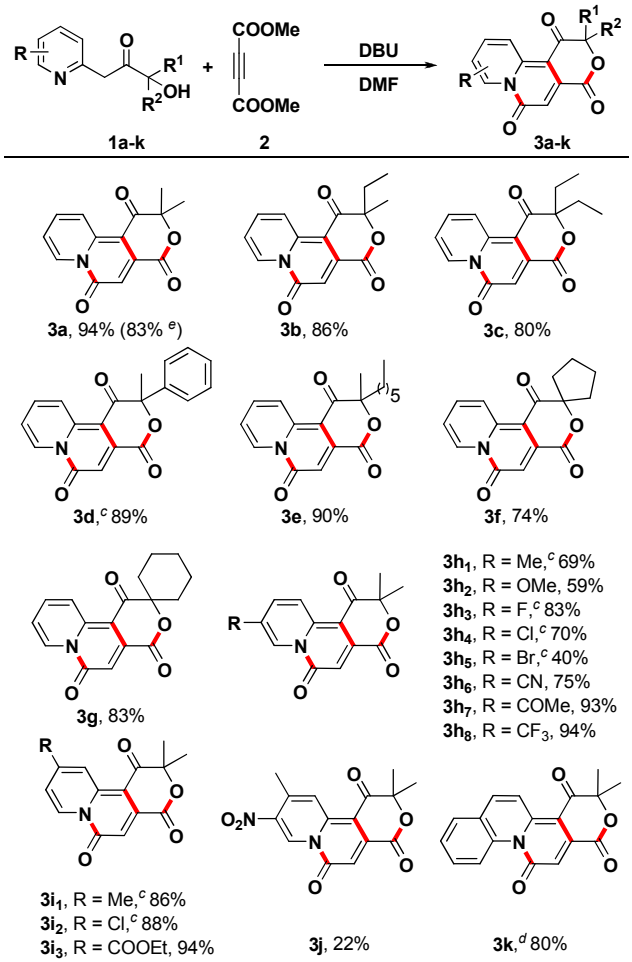
1a **2** **3a**

Entry	Base	Solvent	Temp [°C]	Yield [b] [%]
1	DBU	DMF	50	94
2	DMAP	DMF	50	87
3	DABCO	DMF	50	86
4	DIPEA	DMF	50	58
5	Na_2CO_3	DMF	50	90
6	NaOH	DMF	50	87
7	**DBU**	**DMF**	**rt[c]**	**94**
8	DBU	DMF	rt	85
9	DBU	DMSO	rt	91
10	DBU	MeCN	rt	90
11	DBU	MeOH	rt	35

[a] Reaction conditions: **1a** (0.25 mmol), **2** (0.3 mmol), solvent (1 mL), base (50 mol %), 1 h. [b] Isolated yield. [c] Room temperature. [d] 25 mol % of DBU was used.

With the optimal reaction conditions in hand, we next turned our attention to study the scope of the novel reaction by employing a variety of tertiary α-hydroxy ketones, and the results are presented in Table 2. Gratifyingly, α-hydroxy ketones bearing various R^1 and R^2 substituents on the alkyl chain adjacent to the hydroxyl group underwent smooth transformation to generate the desired tricyclic products in high yields (**3a-e**). The presence of cyclopentyl or cyclohexyl ring led to the formation of spirocyclic products in good yields (**3f-g**). Then we probed the effect of various substituents on the pyridyl ring of the α-hydroxy ketones. It was found that the reaction displayed good tolerance toward a wide range of functional groups (products **3h-i**), including various electron-donating (Me and OMe) and electron-withdrawing substituents (F, Cl, Br, CN, COMe, CF_3, and COOEt) at the 4- or 5-position of 2-pyridyl ring. Comparing the results obtained, substrates with strong electron-withdrawing groups gave the desired products in higher yields than those with weak electron-withdrawing groups or electron-donating groups. Besides, the reaction was sensitive to steric factors. α-Hydroxy ketones with substituents at position 4 of the pyridyl ring showed higher reactive than those with substituents at position 5 (products $\mathbf{3h_1}$, $\mathbf{3h_2}$, $\mathbf{3i_1}$ and $\mathbf{3i_2}$). And 4, 5-disubstituted substrate showed relatively low reactivity, as illustrated by **1j**, which afforded the corresponding product **3j** in only 22% yield. However, 2-quinolinyl substituted α-hydroxy ketone was good substrate, furnishing the corresponding tetracyclic product **3k** in 80% yield although 1 equiv of DBU was necessary. It should be noted that the reaction is not limited to a small scale (0.25 mmol) as it could be conveniently performed on a 5 mmol scale for **1a** affording the desired product **3a** in 83% yield under standard conditions. The structure of the products was confirmed unambiguously by an X-ray crystallographic analysis of a single crystal of **3a** (Fig. 1).[10]

Table 2 Synthesis of pyrano[4,3-*a*]quinolizine-1,4,6(2*H*)-triones from a variety of α-hydroxy ketones[a, b]



[a] Reaction conditions: **1** (0.25 mmol), **2** (0.35 mmol), DBU (50 mol %), DMF (1 mL), room temperature, 1h. [b] Isolated yields. [c] At 50 °C. [d] 1 equiv of DBU was used. [e] 5 mmol scale.

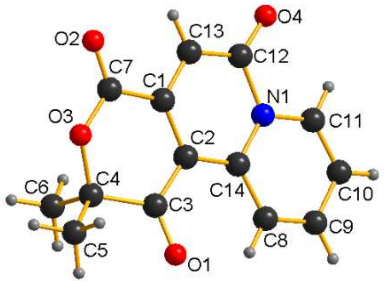
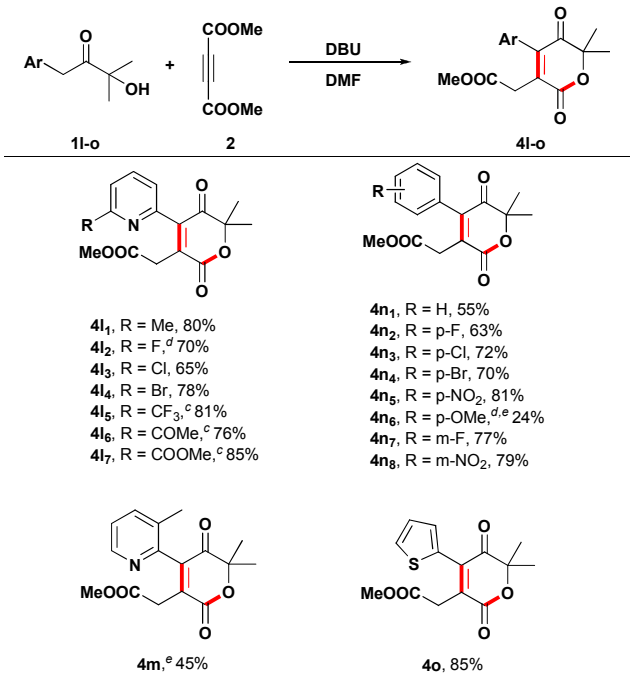


Fig. 1 X-ray structure of **3a**.

Interestingly, when the reaction was carried out with substrates **1l$_1$**, 3-hydroxy-3-methyl-1-(6-methylpyridin-2-yl)butan-2-one, which bears a methyl group at position 6 of pyridine ring, none of the tricyclic product of type **3** was observed even performing the reaction at an elevated temperature (50 °C). However, a 2*H*-pyran-2,5(6*H*)-dione derivative, **4l$_1$**, was isolated in 80% yield. Obviously, the presence of the methyl group at the 6-position of the pyridine ring impeded the nucleophilic attack of pyridyl nitrogen atom to the ester group of **2**. Since the reaction provides a straighforward method for the construction of 2*H*-pyran-2,5(6*H*)-dione motifs, we decided to futher investigated the scope of this transformation and the results are summarized in Table 3.

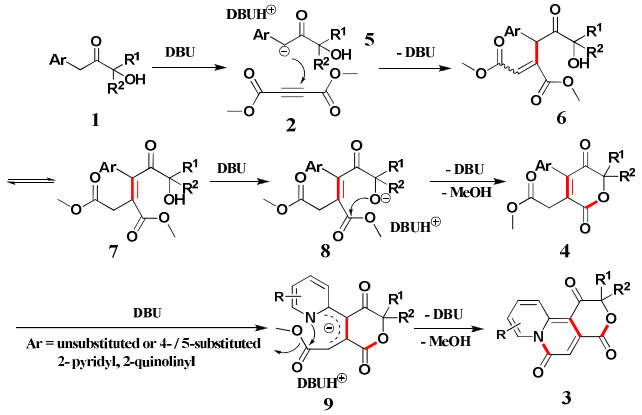
Table 3 Synthesis of 2*H*-pyran-2,5(6*H*)-diones from a variety of α-hydroxy ketones [a, b]



[a] Conditions: **1** (0.25 mmol), **2** (0.4 mmol), DBU (50 mol %), DMF (1 mL), 50 °C, 1h. [b] Isolated yields. [c] At room temperature. [d] 0.5 mmol of **2** was used. [e] The reaction time was 2 h.

As can be seen in Table 3, substrates with a range of functional groups at position 6 of the pyridyl ring reacted smoothly in this manner and furnished 2*H*-pyran-2,5(6*H*)-dione derivatives in moderate to good yields (**4l$_1$-l$_7$**). α-Hydroxy ketones with strong electron-withdrawing substituents, such as fluoro, trifluoromethyl, acetyl and ester group on the pyridyl ring showed high reactive, which could undergo smooth reaction at room temperature. It was also found that substrate with a methyl group at the 3-position of the pyridyl ring also reacted with **2** to give **4m** as a sole product albeit in a low yield (45%). As expected, a variety of phenyl group substituted α-hydroxy ketones were successfully converted into the corresponding products in moderate to good yields (**4n-o**). Again, electron-donating groups on the phenyl ring had a negative effect on the reaction. For example, the presence of a methoxy group at the *para* position of the phenyl ring led to a dramatic decrease in the yield of the desired product (**4n$_6$**) even when the reaction was carried out with 2 equiv of **2** for 2 hours, and large amount of starting material was recovered. Pleasingly, 2-thiophenyl group substituted substrate reacted well with **2** to give rise to the desired product **4o** in 85% isolated yield.

Based on our experimental results and the work previously reported [5c], a plausible mechanism is proposed in Scheme 2. The reaction was initiated by a DBU-promoted Michael addition of α-hydroxy ketone **1** to dimethyl but-2-ynedioate **2** to form intermediate **6**, which then underwent an isomerization to gave intermediate **7**, followed by intramolecular transesterification to give the correspongding product **4** *via* intermediate **8**. If the aryl group of the product **4** is unsubstituted 2-pyridyl, or 4- or/and 5-substituted 2-pyridyl, or 2-quinolinyl group, further cyclization will occur through the nucleophilic attack of the pyridyl nitrogen atom to the ester group under basic conditions, affording the product **3** along with the elimination of a methanol molecule.



Scheme 2 Plausible mechanism.

In conclusion, we have developed a novel and facile synthetic protocol for the straightforward construction of pyrano[4,3-*a*]quinolizine-1,4,6(2*H*)-triones and 2*H*-pyran-2,5(6*H*)-diones *via* a base-promoted cascade annulation reaction of tertiary α-hydroxy ketones and dimethyl but-2-ynedioate. The reaction is characterized by high functional groups tolerance, simple operation and very mild reaction conditions. Further study of the reaction mechanism and applying our methods to the synthesis of other heterocycles are currently underway in our laboratories.

Acknowledgements

We thank the National Basic Research Program of China (973 Program) (2010CB732206), the National Natural Science Foundation of China (21172078), the Guangdong Natural Science Foundation (10351064101000000), and the Fundamental Research Funds for the Central Universities (2013ZM0061) for financial support.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental section and analytical details of the products. See DOI: 10.1039/b000000x/

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10 The crystal data for **3a** (CCDC 1018168) can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.uk/data_request/cif.