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PAPER

Facile and efficient synthesis of quinolin-2(1*H*)-ones *via* cyclization of penta-2,4-dienamides mediated by H_2SO_4†

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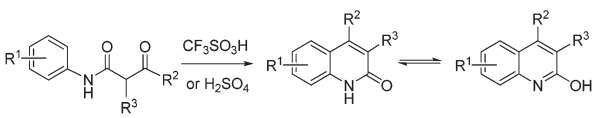
A facile and efficient synthesis of substituted quinolin-2(1*H*)-ones is developed *via* intramolecular cyclization of penta-2,4-dienamides mediated by concentrated H_2SO_4 (98%), and a mechanism involving the formation of a dicationic superelectrophile, and subsequent intramolecular nucleophilic cyclization reactions is proposed.

Introduction

Quinolin-2(1*H*)-ones and their analogues have attracted significant attention since their core structure is present in a number of natural products and synthetic organic compounds along with a broad range of pharmaceutical activities.[1,2] Actually, some substituted quinolin-2(1*H*)-ones have been identified as antibiotics, such as nybomycin and deoxynybomycin,[3] angiotensin II receptor antagonist,[4] antiplatelet agents,[5] glycine NMDA receptor antagonists,[6] endothelin receptor antagonist,[7] and antitumor agents.[8] In addition, functionalized quinolin-2(1*H*)-ones have been used as versatile intermediates in the transformation of other nitrogen-containing heterocycles.[9] So far, extensive work has been directed toward the construction of the skeleton of such heterocycles.[10] The classical procedures for the synthesis of quinolin-2(1*H*)-ones include acid-catalyzed Knorr synthesis (Scheme 1),[11] base-catalyzed Friedländer synthesis[12] and the homogeneous metal-catalyzed heteroannulation of acyclic precursors.[13] Other synthetic methods associated with microwave[14] or irradiation[15] have also been reported. Nevertheless, the development of efficient synthetic approaches for such heterocycles has been focus of intense research for decades and continues to be an active area of research today.



Scheme 1 Reactions of β-oxo amides under acidic conditions.

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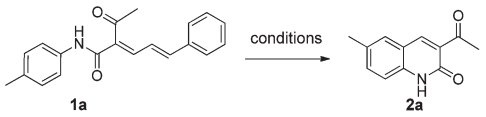
Results and discussion

During the course of our studies on the synthetic utility of 1,3-dicarbonyl compounds, we found that the easily available β-oxo amides and their derivatives showed fascinating structural features as versatile organic intermediates, and based on which, we developed a range of synthetic approaches to construct aromatic and heterocyclic ring skeletons.[16] In connection with these studies and our continuing interest in the synthesis of highly valuable heterocycles, we synthesized a series of penta-2,4-dienamides from β-oxo amides and examined their reaction behaviors toward acidic conditions. By this study, we achieved an efficient synthesis of substituted quinolin-2(1*H*)-ones mediated by concentrated H_2SO_4 (98%). Herein, we wish to report our experimental results and present a proposed mechanism involved in the cyclization reaction.

The substrates, penta-2,4-dienamides **1**, were prepared by Knoevenagel condensation of commercially available β-oxo amides with cinnamaldehydes in the presence of piperidine in high yields according to a procedure described in literature.[17] We selected 2-acetyl-5-phenyl-*N*-*p*-tolylpenta-2,4-dienamide **1a** as a model compound to investigate its reaction behavior under acidic conditions. Thus, the reaction of **1a** and triflic acid (CF_3SO_3H) was first attempted at room temperature. As indicated by TLC, the reaction occurred and furnished a predominant product after work-up and purification by column chromatography of the resulting mixture. The product was characterized as 3-acetyl-6-methyl quinolin-2(1*H*)-one **2a** on the basis of its spectral and analytical data (Table 1, entry 1).

The results encouraged us to explore the reaction conditions with the aim of optimizing the yield of **2a**. It was observed that the reaction of **1a** with CF_3CO_2H resulted in very low conversion (Table 1, entry 2). In the presence of $TiCl_4$, the reaction turned out to be a complex mixture with **2a** as a main product (Table 1, entry 3). No reaction occurred when **1a** was treated with $SnCl_4{\cdot}5H_2O$ in CH_2Cl_2 or 50% aqueous H_2SO_4 at room temperature (Table 1, entries 4 and 5). Interestingly, when **1a**

Table 1 The reaction of **1a** under different acidic conditions[a]

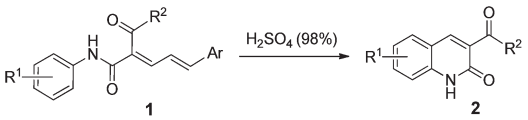


Entry	Conditions	Temp. (°C)	Time (h)	Yield[b] (%)
1	CF_3SO_3H	r.t.	5.0	54
2	CF_3COOH	r.t.	5.0	23[c]
3	$TiCl_4/CH_2Cl_2$	r.t.	10.0	31
4	$SnCl_4{\cdot}5H_2O/CH_2Cl_2$	r.t.	5.0	No reaction
5	H_2SO_4 (50%)	r.t.	5.0	No reaction
6	H_2SO_4 (98%)	r.t.	3.0	89
7	H_2SO_4 (98%)	50	1.5	91
8	H_2SO_4 (98%)	80	1.0	90

[a] Reaction conditions: (i) for entries 1, 2 and 5–8: **1a** (2.0 mmol), acid (5.0 mL); (ii) for entries 3 and 4: **1a** (2.0 mmol), acid (4.0 mmol), CH_2Cl_2 (10.0 mL). [b] Isolated yield. [c] 58% of **1a** was recovered.

was subjected into concentrated H_2SO_4 (98%, aq) at room temperature, the reaction proceeded smoothly and gave **2a** in 89% yield (Table 1, entry 6). Further experimental results revealed that increase of the reaction temperature had no significant influence on the yield of **2a**, but accelerated the reaction rate (Table 1, entries 7 and 8).

Table 2 Synthesis of substituted quinolin-2(1*H*)-ones **2**[a]



Entry	1	R^1	R^2	Ar	2	Yield[b] (%)
1	**1a**	4-Me	Me	C_6H_5	**2a**	89
2	**1b**	H	Me	C_6H_5	**2b**[c]	81
3	**1c**	2-Me	Me	C_6H_5	**2c**	82
4	**1d**	3-Me	Me	C_6H_5	**2d**	79
5	**1e**	2,4-Me_2	Me	C_6H_5	**2e**	80
6	**1f**	4-Cl	Me	C_6H_5	**2f**	83
7	**1g**	4-MeO	Me	C_6H_5	**2g**	86
8	**1h**	2-MeO	Me	C_6H_5	**2h**	82
9	**1i**	2,5-$(MeO)_2$,3-Cl	Me	C_6H_5	**2i**	85
10	**1j**	4-Me	C_6H_5	C_6H_5	**2j**	79
11	**1k**	H	C_6H_5	C_6H_5	**2k**[d]	81
12	**1l**	H	*n*-Pr	C_6H_5	**2l**	76
13	**1m**	2-Me	Me	4-$MeOC_6H_4$	**2c**	83

[a] Reagents and conditions: **1** (2.0 mmol), H_2SO_4 (98%, aq, 5.0 mL), r.t., 2.0–3.0 h. [b] Isolated yield. [c] See ref. 9*e*. [d] See ref. 10*e*.

Under identical conditions as for **2a** in Table 1 entry 6, a series of reactions of penta-2,4-dienamides **1b-l** were carried out in concentrated H_2SO_4 (98%, aq) at room temperature, and some of the results are summarized in Table 2. The versatility of the cyclization reaction proved to be suitable for **1b-l** to afford the corresponding substituted quinolin-2(1*H*)-ones **2b-l** in good yields (Table 2, entries 2–12). In the case of **1d**, 3-acetyl-7-methyl quinolin-2(1*H*)-one **2d** was exclusively obtained in 79% yield, which suggested that the cyclization reaction of **1d** proceeded in a regioselective manner (Table 2, entry 4). It is worth mentioning that the structure of **2l** was elucidated by means of the X-ray single crystal analysis (Fig. 1) and further confirmed by its spectral and analytical data. The quinolin-2(1*H*)-one synthesis was further evaluated by performing penta-2,4-dienamide **1m** with concentrated H_2SO_4 (98%, aq) at room temperature, in which 3-acetyl-8-methylquinolin-2(1*H*)-one **2c** was obtained in 83% yield (Table 2, entry 13). To extend the scope of this quinolin-2(1*H*)-one synthesis, we prepared *N*,5-diphenylpenta-2,4-dienamide **1n**[18] and subjected it to concentrated H_2SO_4 (98%, aq) at room temperature. Unfortunately, the reaction resulted in a complex mixture, and the desired product **2n** was even not detected by means of NMR spectroscopy. This result suggested that the acyl group of substrate **1** is essential to the above intramolecular cyclization reaction. Nevertheless, all the above results demonstrated the efficiency and synthetic interest of the quinolin-2(1*H*)-one synthesis with respect to penta-2,4-dienamides **1** bearing variable R^1 and R^2 substituted groups in concentrated H_2SO_4. Therefore, we provide a novel and convenient synthetic approach for quinolin-2(1*H*)-one of type **2**.

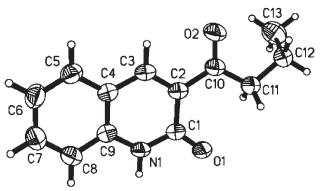
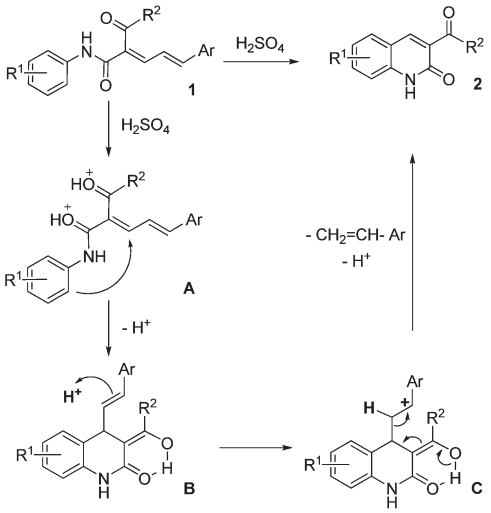


Fig. 1 ORTEP drawing of **2l**.

To gain insight into the mechanism for the quinolin-2(1*H*)-one synthesis, the extract of the resulting mixture from reaction of **1m** was conducted on high resolution mass spectrometer. On the mass spectra, the peak at 202.0886 ($[M + 1]^+$) was detected for product **2c**, and the peak at 135.0853 was assigned to the molecular ion ($[M + 1]^+$) of *p*-methoxystyrene. In addition, the peaks at 109.1030 and 131.9634 appeared could be assigned to $[M + 1]^+$ and $[M + Na]^+$ ions of anisole, molecular fragment of *p*-methoxystyrene, respectively. These findings provided direct evidences for the mechanism for the cyclization of penta-2,4-dienamides **1**.

In this work, penta-2,4-dienamides **1** were found to undergo an intramolecular cyclization in a chemoselective manner since the nucleophilic addition site was on the β-carbon of the α,β-unsaturated carbonyl compounds **1** instead of their acyl group. Apparently, the synthesis of quinolin-2(1*H*)-ones of type **2** is different from the conventional acid-catalyzed Knorr quinolin-2(1*H*)-one synthesis. During the 1960s and 1970s, a number of cationic electrophilic reagents were noted to show greatly enhanced reactivity in the presence of superacids, which led to the concept of superelectrophilic activation.[19] In 1964, Staskun observed that both the acid strength and the acid quantity were important to the Knorr cyclization, and proposed a superelectrophilic dication mechanism, which subsequently appeared in reviews and books on heterocyclic chemistry.[20] Although admirable as a predecessor of the general concept of

superelectrophilic activation, the mechanism proposed by Staskun is questionable. At the time of that study, there was a considerable amount of uncertainty regarding the site of protonation on amides.[21] This question has been resolved over the years and in most cases oxygen is preferred over nitrogen as the site of protonation. Recently, Sai *et al.* investigated the acid-catalyzed Knorr cyclization by experimental and computational methods, and revealed that β-oxo amides underwent diprotonation at oxygen atom of the two carbonyl groups to generate distonic superelectrophiles, which triggered the cyclization chemistry.[22]



Scheme 2 Plausible mechanism of the synthesis of quinolin-2(1*H*)-ones **2**.

On the basis of our obtained results combined with the reported literature,[22,23] a plausible mechanism for the synthesis of quinolin-2(1*H*)-ones **2** is presented in Scheme 2. Mediated by H_2SO_4 (98%, aq), penta-2,4-dienamide **1** is protonated to generate dicationic superelectrophiles **A**, which undergoes intramolecular cyclization to afford intermediate **B**. Then, a carbocation **C** is formed through protonation of the carbon–carbon double bond of **B**,[24] which is finally converted into quinolin-2(1*H*)-one **2** along with the elimination of a vinyl arene.

Conclusions

In summary, a facile and efficient one-pot synthesis of substituted quinolin-2(1*H*)-ones of type **2** is developed from penta-2,4-dienamides **1** mediated by concentrated H_2SO_4. The simple execution, readily available substrates, good yields, and wide range of synthetic potential of the products make this protocol much attractive. The extension of the scope of the methodology and the further research of the mechanism are currently under investigation in our laboratory.

Experimental

General

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C at 300 MHz and 100 MHz, respectively, with TMS as internal standard. IR spectra (KBr) were recorded on FTIR-spectrophotometer in the range of 400–4000 cm^{-1}. All melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected. Mass spectra were recorded on Agilient 1100 LCMsD mass spectrometer.

Typical procedure for the synthesis of products 2

Typical procedure for the synthesis of substituted quinolin-2(1*H*)-ones **2** (**2a** as an example): To a 50 mL round bottomed flask was added **1a** (0.61 g, 2.0 mmol) and 98% concentrated H_2SO_4 (5.0 mL). The mixture was stirred at room temperature for 3.0 h. After the substrate **1a** was consumed as indicated by TLC, the mixture was poured into ice water, and then extracted with dichloromethane (3 × 20 mL), the combined organic phase was washed with water (3 × 20 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (silica gel, petroleum ether : ethyl acetate 8 : 1) to give **2a** as white solid (0.36 g, 89%).

3-Acetyl-6-methylquinolin-2(1*H*)-one (2a)

White solid: mp 236–238 °C; ^{1}H NMR (300 MHz, DMSO): δ 2.34 (s, 3H), 2.61 (s, 3H), 7.26 (d, J = 8.4 Hz, 1H), 7.44 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 1H), 7.65 (s, 1H), 8.37 (s, 1H), 12.03 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 20.28, 30.60, 114.90, 118.00, 129.26, 131.37, 134.29, 138.54, 142.68, 160.32, 197.42; IR (KBr, cm^{-1}): 3138, 2865, 1683, 1660, 1559, 1500, 1453, 1213, 603; Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.85; H, 5.66; N, 7.03.

3-Butyrylquinolin-2(1*H*)-one (2l)

White solid: mp 196–198 °C; ^{1}H NMR (300 MHz, DMSO): δ 0.91 (t, J = 7.2 Hz, 3H), 1.54–1.64 (m, 2H), 3.07 (t, J = 7.2 Hz, 2H), 7.23 (t, J = 7.2 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.59–7.65 (m, 1H), 7.86 (d, J = 7.5 Hz, 1H), 8.43 (s, 1H), 12.12 (s, 1H); ^{13}C NMR (150 MHz, DMSO): δ 13.66, 16.99, 44.03, 114.98, 118.14, 122.28, 129.64, 129.92, 132.67, 140.28, 142.69, 160.28, 200.06; IR (KBr, cm^{-1}): 3440, 2955, 1676, 1660, 1549, 1489, 794, 754, 737; Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.42; H, 6.01; N, 6.59.

Crystal data for **2l**: $C_{13}H_{13}NO_2$, white crystal, M = 215.24, triclinic, $P\bar{1}$, a = 5.5086(4) Å, b = 8.9755(7) Å, c = 11.5642(9) Å, α = 103.510(1)°, β = 95.810(1)°, γ = 101.073(1)°, V = 539.16(7) Å^3, Z = 2, T = 185 K, $F000$ = 228.0, $F000'$ = 228.11, R = 0.0432(1775), wR_2 = 0.1239(2076). CCDC deposition number: 870320.

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