Gas-Phase Pyrolysis in Organic Synthesis: Rapid Green Synthesis of 4-Quinolinones

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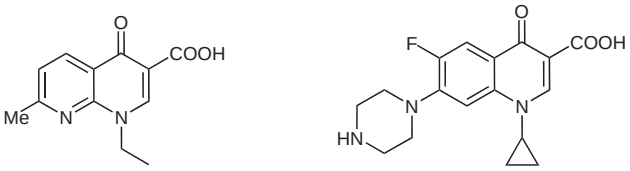
Abstract: Gas-phase pyrolysis of aminomethylene Meldrum's acid derivatives gave quinolinones and/or amines depending on the nature of arylamino moiety. Effect of substituent on reaction rate and nature of pyrolysis products supports the suggested intramolecular nucleophilic substitution reaction via initially formed ketene-amine intermediate.

Key words: Meldrum's acid, pyrolysis, 4-quinolinones

The rapid rise in bacterial resistance to traditional antibiotic such as β-lactams has encouraged continuous search for new classes of antibiotics, which led to introduction of nalidixic acid (**1**) in 1962. Ciprofloxacin (**2**, Figure 1) was marketed in 1980; however, recently there has been a rapid development of resistance to ciprofloxacin. These searches for new quinolin-4-ones[1,2] were initiated by synthesis of either via cyclization β-aminoacrylates,[3] high-temperature condensation of β-ketoesters with amines,[4] or via reaction of diethyl ethoxymethylenemalonates with aromatic amines.[5] These are multistage routes and are of limited scope.

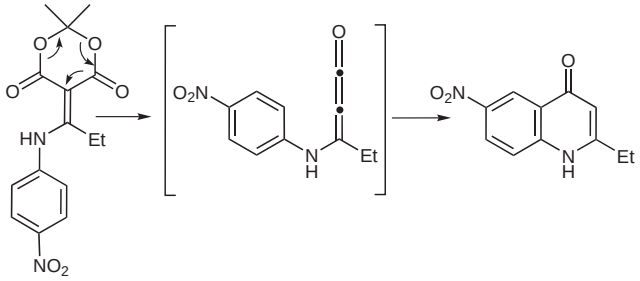


1 2

Figure 1

Chen and Wang have reported the formation of 4-quinolinones[6] upon heating **3** in diphenyl ether at 250 °C.[6,7] It was suggested[6] that the reaction does not involve electrophilic attack on the benzene ring but rather an electrocyclization of 3-(paranitrophenylamino)penta-1,2-dien-1-one (**4**,[7] cf. Scheme 1).

In conjunction with our research interest in the utility of gas-phase pyrolytic reactions as green benign approaches in organic synthesis[8–10] we describe in this article an efficient synthesis of quinolin-4-one from Meldrum's acid derivatives.



3 4 5

Scheme 1

Ten Meldrum's acid derivatives were synthesized utilizing the reported synthetic approach[11] via condensing Meldrum's acid **6** with triethylorthoformate and aromatic amines **7** to produce **8a**–**j** (Scheme 2).[11] Static gas-phase pyrolysis[12] of **8a**–**j** at 300 °C for 900 s resulted in the formation of aromatic amines in addition to quinolinones **11** and acetone, however, in flash vacuum pyrolysis (FVP)[13] at 600 °C and 10^{-2} Torr only quinolinones, acetone, and trace amount of aromatic amines are produced. The yield of each product was found to depend on the nature of the substituent on the benzene ring as well as pyrolysis conditions (cf. Table 1). Pyrolysis of **8a**–**c** either by FVP at 600 °C[13] or by static pyrolysis at 300 °C afforded quinolinones **11a**–**c**, acetone, and trace amount of aromatic amines. The analyses of the product **11b** as an example are in agreement with the proposed structure.[14] Pyrolyzing **8d** afforded, in addition to quinolinone **11d** and amine **7d**, quinolinone **11a** which results most likely via ipso substitution. On the other hand, pyrolysis of **8e**–**h** under the same conditions offered in addition to acetone a 1:1 mixture of quinolinones **11e**–**h** and **11i**–**l**. The structure of **11e** and **11i** was established based on spectral data.[15,16]

Contradicting with reported formation of 2-methyl quinolinones upon pyrolyzing **3** in diphenyl ether,[6] in our hands pyrolysis of **8i** afforded only traces of quinolinones **11m** in addition to acetone. The major pyrolysis product, in fact, was 4-nitroaniline. This confirms that the electron density at the cyclization reaction site plays a significant role in the course of the cyclization reaction. Thus substituents in **8a**–**c** generally enrich the π-electronic cloud in the benzene ring, while a nitro substituent in **8i** is known to decrease the π-cloud density in the ring, thus reducing the nucleophilicity of the ring carbons. We thus believe that the initially formed **9** either cyclizes into **10** that then

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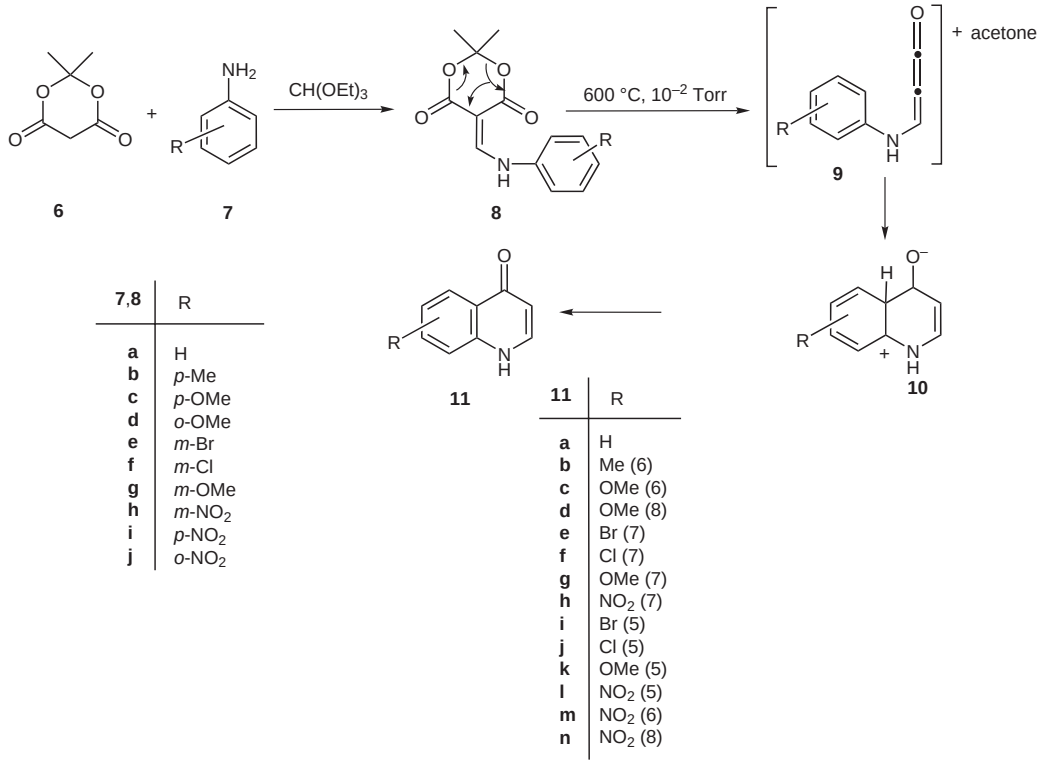


7,8	R
a	H
b	*p*-Me
c	*p*-OMe
d	*o*-OMe
e	*m*-Br
f	*m*-Cl
g	*m*-OMe
h	*m*-NO_2
i	*p*-NO_2
j	*o*-NO_2

11	R
a	H
b	Me (6)
c	OMe (6)
d	OMe (8)
e	Br (7)
f	Cl (7)
g	OMe (7)
h	NO_2 (7)
i	Br (5)
j	Cl (5)
k	OMe (5)
l	NO_2 (5)
m	NO_2 (6)
n	NO_2 (8)

Scheme 2

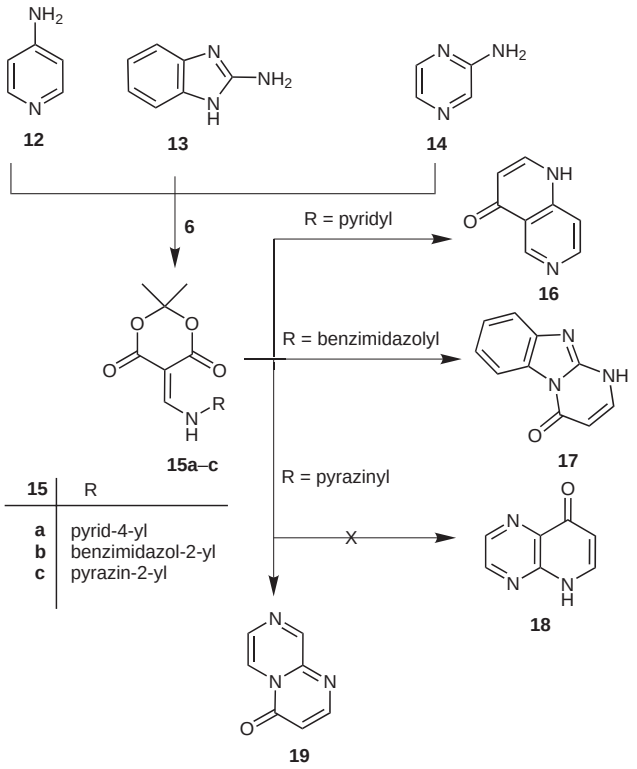
Table 1 Pyrolysis of Compounds **8**

Reactant	Product yield (%)	
	Flash vacuum pyrolysis	Static pyrolysis
8a	**11a** (83.5%)	**11a** (35.6%)
8b	**11b** (65.2%) + **7b** (1%)	**11b** (53%) + **7b** (36%)
8c	**11c** (14.5%) + **7c** (5%)	**11c** (51.3%) + **7c** (17.7%)
8d	**11d** (20. 1%) + **11a** (5.6%) + **7d** (2.3%)	**11d** (15.8%) + **11a** (18%) + **7d** (26.1%)
8e	**11e** (14.9%) + **11i** (18%)	**11e** (14.1%) + **11i** (27.7%)
8f	**11f** (14.3%) + **11j** (15.2%)	**11f** (34%) + **11j** (20%)
8g	**11g** (17%) + **11k** (18.8%)	**11g** (10.1%) + **11k** (11.7%)
8h	**11h** (11.4%) + **11l** (21.6%) + **7h** (33%)	**11h** (1.7%) + **11l** (2.5%) + **7h** (28.2%)
8i	**11m** (2.9%) + **7i** (9.9%)	**11m** (1%) + **7i** (12%)
8j	**11a** (9.6%) + **11n** (21%) + **7j** (3.5%)	**11a** (%) + **11n** (%) + **7j** (%)
15a	**16** (17.8%) + **12(**2%)	**16** (9%) + **12(**23%)
15b	Did not sublime	**17** (16.5%)
15c	**19** (84.8%)	**19** (21.6%)

affords **11**, or is decomposed prior to cyclization when the cyclization site is not sufficiently nucleophilic. Similar to compound **8c**, compound **8j** undergoes ipso substitution to give a mixture of **11n** and **11a**. It is worth mentioning here that the attack at ipso position is well known for nitro substituents but we believe that it is quite unusual with methoxy substituents.[17] Our conclusion is that formation of quinolinones via pyrolysis of **8a**–**j** proceeds via an

intramolecular nucleophilic displacement. Although the fact that **8h** is formed in better yield than **8i** seems at first sight contradictory to this assumption, closer inspection reveals that this is not exactly the case, as substitution in *para*-position would contribute to the ease of N–N cleavage and this contributes to the observed low yield of **8i**.

We have then investigated the possible utility of this reaction for synthesis of condensed azines, by condensing **6** with heterocyclic amines **12**–**14**. The reaction produced **15a**–**c** in good yields. The FVP of **15a**,**b** at 600 °C afforded the condensed azines **16** and **17**. On the other hand, FVP of **15c** gave a product that can in theory be formulated as pyrido[2,3-*b*]pyrazine (**18**), or pyrazino[1,2-*a*]pyrimidine (**19**). The structure of **19** was established based on the absence of D_2O exchangeable NH signal[18] (cf. Scheme 3).



Scheme 3

A simple, green approach for synthesis of quinolinones, azoloazines, and pyrimidoazines is now available. Moreover we were able provide evidence that the conversion of **8** into **11** processes via an intramolecular nucleophilic substitution reaction for which substituents on the aryl moiety play an important role.

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(12) **Static Pyrolysis of 8–j**
The substrate (0.2 g) was introduced in the Pyrex reaction tube (12 cm length and 1.5 cm internal diameter). The tube was sealed under vacuum (0.02 m bar) and placed in the pyrolyzer for 900 s at 300 °C. The content of the tube was then separated by preparative high-performance liquid chromatography (HPLC) and was analyzed by ^{1}H NMR, ^{13}C NMR, IR and GC-MS. Relative and percent yields were determined from NMR.
(13) **Flash Vacuum Pyrolysis of 8a–j**
The sample was volatilized from a tube in a Buchi Kugelrohr oven through a 30 × 2.5 cm horizontal-fused quartz tube and was heated externally by a cabolite Eurotherm tube furnace MTF-12/38A to 600 °C. The products were collected in a U-shaped trap cooled in liquid nitrogen. The whole system was maintained at a pressure of 10^{-2} Torr by an Edwards Model E2M5 high-capacity rotary oil pump, the pressure being measured by a Pirani gauge situated between the cold trap and pump. Under these condition the contact time in the hot zone was estimated to be 10 ms. Products collected in the U-shaped trap were analyzed by ^{1}H NMR, ^{13}C NMR, IR and GC-MS. Relative and percent yields were determined from NMR.
Compounds **11a**,**c**,**d**,**f**–**h**,**j**–**n**, **16**, and **17** has been reported earlier and proved to be identical with products obtained here.[19–27]
(14) **6-Methyl-1*H*-quinolin-4-one (11b)**
Mp 240–242 °C. IR (KBr): 3050 (NH), 1625 (CO) cm^{-1}. LC-MS: *m*/*z* (%) = 159 (100) [M$^+$]. ^{1}H NMR (400 MHz, DMSO): δ = 2.39 (s, 3 H, CH_3), 6.0 (d, 1 H, *J* = 7.2 Hz, quinoline-H3), 7.45 (d, 1 H, quinoline-H8), 7.48 (d, 1 H, quinoline-H7), 7.86 (d, 1 H, *J* = 7.2 Hz, quinoline-H2), 8.31 (s, 1 H, quinoline-H5), 11.72 (br s, 1 H, D_2O exchangeable, NH). ^{13}C NMR (DMSO, 100 MHz): δ = 21.55, 109.09, 119.18, 124.70, 125.96, 134.31, 134.57, 138.67, 140.50, 178.48. DEPT 135: δ = 21.55, 109.09, 119.18, 124.70, 125.96, 134.57, 140.50.

(15) **7-Bromo-1*H*-quinolin-4-one (11e)**
Mp 242–244 °C. LC-MS: *m*/*z* = 225 [M + 1]. ^{1}H NMR (400 MHz, DMSO): δ = 6.04 (d, 1 H, H3, *J* = 7.37 Hz), 7.52 (d, 1 H, *J* = 8.56 Hz), 7.74 (s, 1 H, H-5), 7.82 (d, 1 H, *J* = 7.37 Hz, H2), 8 (d, 1 H, *J* = 8.56 Hz, H6), 11.22 (br, 1 H, NH). ^{13}C NMR (100 MHz, DMSO): δ = 111.5, 120.4, 123.2, 126, 128.4, 132.7, 141, 143.4, 177.4.

(16) **5-Bromo-1*H*-quinolin-4-one (11i)**
Mp 234–236 °C. IR (KBr): 1645 (CO) cm^{-1}. LC-MS: *m*/*z* = 225 [M + 1]. ^{1}H NMR (400 MHz, DMSO): δ = 6.06 (d, 1 H, H3, *J* = 7.24 Hz), 7.41–7.47 (m, 3 H, ArH), 7.93 (d, 1 H, *J* = 7.24 Hz, H-2), 11.18 (br, 1 H, NH). ^{13}C NMR (75 MHz, DMSO): δ = 110.3, 119.5, 121.5, 125.6, 127.2, 130.6, 139.3, 142, 177.

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(18) **Pyrazino[1,2-*a*]pyrimidin-4-one (19)**
Mp 178–180 °C. IR (KBr): 1692 (CO) cm^{-1}. LC-MS: *m*/*z* = 148 [M + 1]. ^{1}H NMR (400 MHz, DMSO): δ = 6.67 (d, 1 H, *J* = 6.44 Hz, pyrimidine-H), 8.19 (d, 1 H, *J* = 4.64 Hz, pyrazine-H), 8.41 (d, 1 H, *J* = 6.44 Hz, pyrimidine-H), 8.73 (d, 1 H, *J* = 4.64 Hz, pyrazine-H), 9.13 (s, 1 H, pyrazine-H). ^{13}C NMR (75 MHz, DMSO): δ = 109.6, 118.2, 133.0, 145.8, 154.2, 155.9, 156.8. DEPT 135: δ = 109.6, 118.2, 133.0, 154.2, 155.9. Anal. Calcd for $C_7H_5N_3O$ (147.14): C, 57.14; H, 3.43; N, 28.56. Found: C, 57.53; H, 3.62; N, 28.83.

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