Regioselective Synthesis of Quinolin-4-ones by Pyrolysis of Anilinomethylene Derivatives of Meldrum's Acid

Lawrence Hill,[a] S. Haider Imam,[a] Hamish McNab,*[b] William J. O'Neill[b]

[a] Durham Organics Ltd., Units 12-14, Langley Moor Industrial Estate, Langley Moor, Durham, DH7 8JE, UK

[b] School of Chemistry, The University of Edinburgh, West Mains Road, Edinburgh, EH9 3JJ, UK
Fax +44(131)6504743; E-mail: H.McNab@ed.ac.uk

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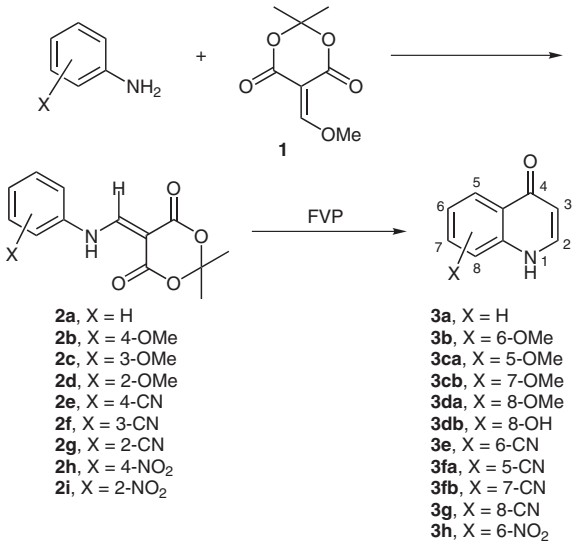
Abstract: Electron-rich and electron-deficient anilinomethylene derivatives of Meldrum's acid cyclize equally efficiently to quinolin-4-ones via imidoylketene intermediates under flash vacuum pyrolysis (FVP) conditions.

Key words: quinolin-4-ones, Meldrum's acid, flash vacuum pyrolysis

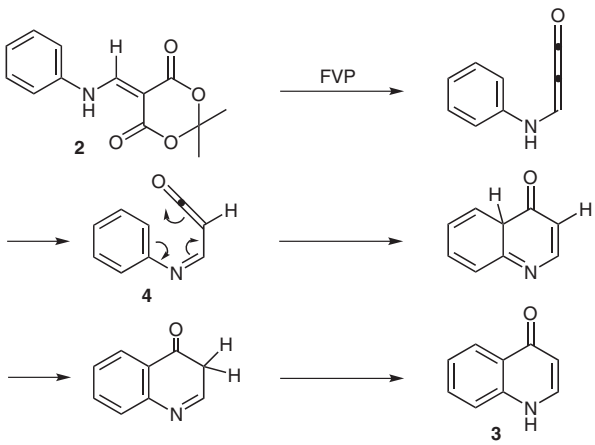
The synthesis of quinolin-4-ones **3** by pyrolysis of anilinomethylene derivatives of Meldrum's acid **2** is well established in solution[1] and in the gas phase under flash vacuum pyrolysis (FVP) conditions (Scheme 1).[2–4] However, a paper in this journal[5] recently reported only very low NMR yields of quinolinones **3** for FVP reactions of substituted derivatives of **2**; side products included recovery of the aniline starting material (up to 33%),[5] and in some cases the parent quinolinone was formed by loss of the substituent (up to 9.6%).[5] Very little selectivity was observed when a *meta*-substituted starting material was used.[5] Finally, the mechanism proposed[5] for the cyclization is at variance from the accepted view of this process (Scheme 2)[4] involving electrocyclization of an imidoylketene **4**. Such intermediates have been identified by matrix isolation studies carried out by the Wentrup group.[4,6]

In this paper we present some of our FVP results[7] in this field. These show significantly improved yields of quinolin-4-ones **3** on a 'preparative' scale (0.3 g or above) compared with those reported,[5] and significantly improved selectivity for *meta*-substituted examples, leading to reasonable preparative routes to 7-substituted isomers. We report deuterium labeling results which support the accepted mechanism (Scheme 2) and not that suggested in ref. 5 and finally we back up these results by DFT calculations which complement those on imidoylketene cyclizations previously reported.[8]

We illustrate these points, first, by consideration of the FVP reactions of the three methoxy compounds **2b–d**. The precursors **2** were made in high yield by reaction of the appropriate aniline derivative with methoxymethylene Meldrum's acid (**1**) in acetonitrile at room temperature.[9,10] In each case, the FVP reactions gave solid products and the aromatic region of the ^{1}H NMR spectra of the entire crude pyrolysates are shown in Figures 1– 3. These spectra demonstrate that, in our hands, the reactions proceed exceptionally cleanly to a quinolinone **3** with minimal byproducts. Thus, FVP of the *p*-methoxy derivative **2b** at 500 °C provides 6-methoxyquinolin-4-one (**3b**, Figure 1);[11] the isolated yield on a 0.5 g scale is 61% after recrystallization.[12] In contrast, the previous authors quote an NMR yield of **3b** of just 14.5% with some 5% *p*-anisidine byproduct.[5]



Scheme 1



Scheme 2

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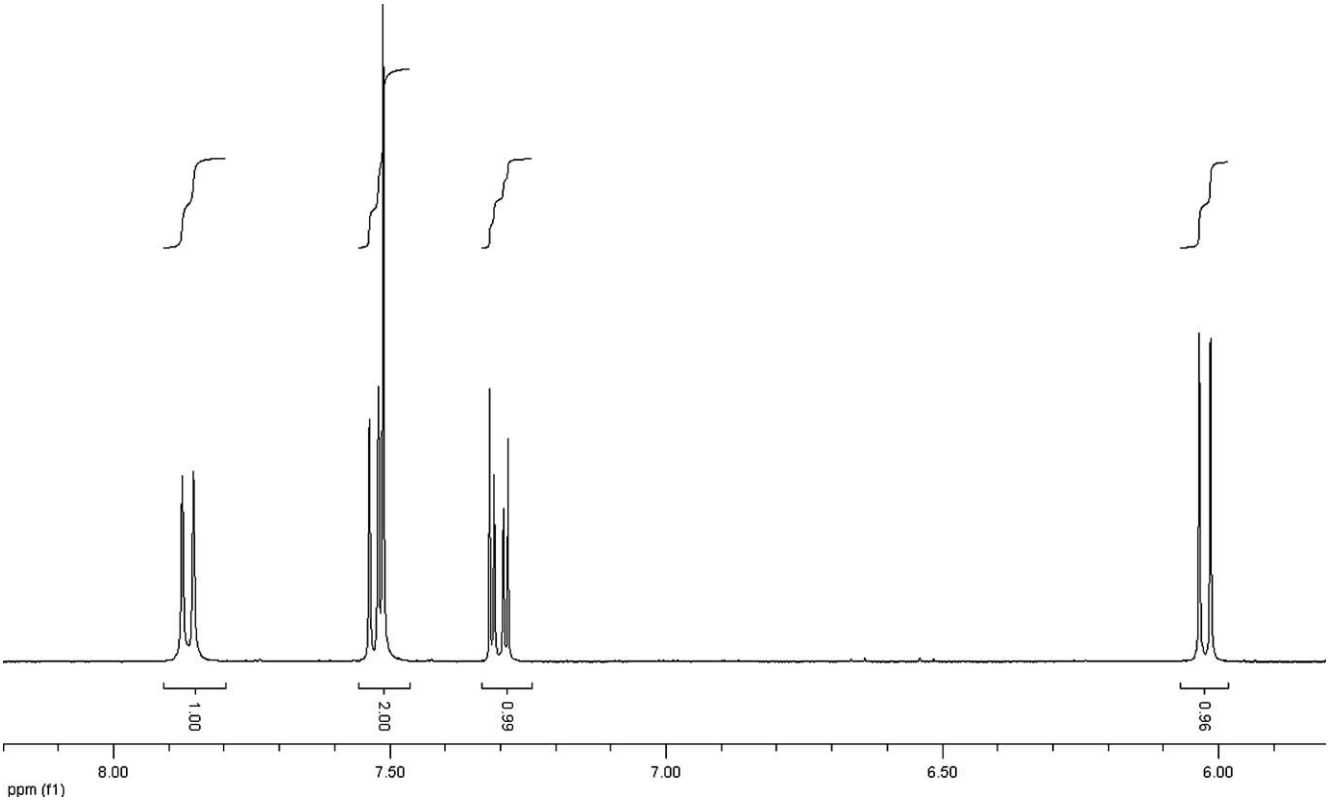


Figure 1 Aromatic region of the ^{1}H NMR spectrum (360 MHz, DMSO-d_6) of the entire pyrolysate from **2b** (500 °C), showing formation of a single product, 6-methoxyquinolin-4-one (**3b**)[11,12]

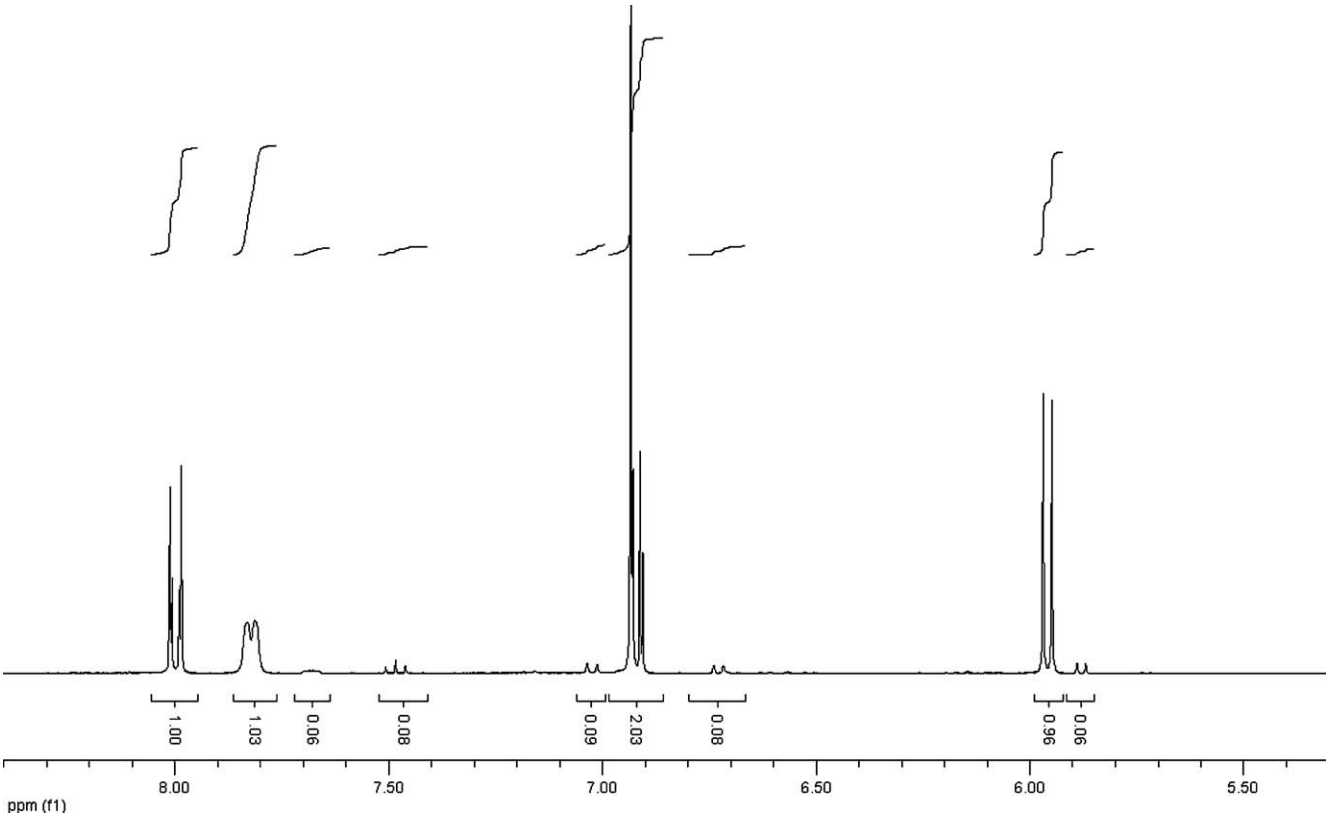


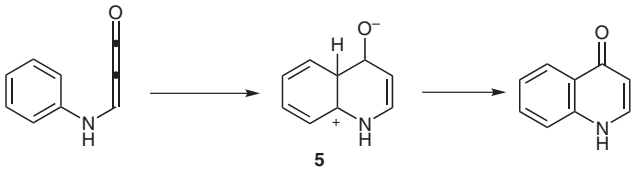
Figure 2 Aromatic region of the ^{1}H NMR spectrum (360 MHz, DMSO-d_6) of the entire pyrolysate of **2c** (500 °C), showing 7-methoxyquinolin-4-one (**3cb**) as the major product; minor peaks at δ = 7.68, 7.48, 7.02, 6.73, 5.88 ppm are due to the 5-methoxy isomer

The previous authors[5] reported a mixture of 5- and 7-methoxyquinolin-4-one [**3ca** (18.8%) and **3cb** (17%), respectively, i.e., the 5-isomer was marginally the major product] by FVP of the *m*-methoxy derivative **2c**. In our hands, FVP of **2c** at 500 °C provides the 7-isomer **3cb**[11] as the major product (**3cb**/**3ca** = 93:7; Figure 2). Compound **3cb** can be obtained pure by one recrystallization of the crude pyrolysate (62%).[12]

FVP of the *o*-methoxy compound **2d** at 500 °C gives the 8-methoxyquinolin-4-one **3da** (99%) exclusively (Figure 3).[12] At higher temperatures (650 °C) an impurity is formed which was identified as the 8-hydroxy-compound **3db** by comparison with an authentic sample, and not **3a** as claimed by the previous authors.[5] Homolysis of the Me–O bond of aromatic methoxy compounds (and hydrogen atom capture by the resultant phenoxyl radical) is well known under FVP conditions, but not usually at such a low temperature.[14]

On the basis of poor results of the pyrolyses of the electron-deficient nitro compounds, e.g., **2h** and **2i**, the earlier authors have proposed the mechanism shown in Scheme 3 in which nucleophilic attack on the methyleneketene intermediate is the key step.[5] We now show[15] that FVP of the cyano derivatives **2e**–**g** provide the quinolinones **3e** (94%), **3fa**, and **3fb** (94% combined, **3fb**/**3fa** = ca. 75:25), and **3g** (64%), respectively, as efficiently as the methoxy analogues. The electronic nature of the aromatic ring is therefore not a defining feature of the cyclization mechanism.

The especially poor results noted[5] for the nitro derivatives (e.g., **2h** and **2i**), are not due to the electron-withdrawing nature of the substituent, but instead a combination of factors is involved. First, the substrates are poorly volatile and may decompose at the sublimation stage if the temperature of the inlet is not well controlled. Second, the nitro group has a well-documented pyrolysis chemistry;[19] indeed, FVP of the *o*-nitro compound **2i** leads to quinolin-4-one (**2a**, 31%), quinoxaline-*N*-oxide **6** (12%; by attack of the imidoylketene on the nitro group and loss of CO_2) and 2-nitroaniline (3%) as the main products. Pyrolysis of the *p*-nitro compound **2h** gives 6-nitroquinolin-4-one (**3h**) as the sole isolated product (66%).[20]



Scheme 3

The bonding around C2 and C3 in the zwitterion intermediate **5** is unclear in the mechanism (Scheme 3) proposed by the authors of ref. 5, but the NH appears to remain in place throughout. By FVP of the deuteriated compound **2a′** (Figure 4), we have shown that this mechanism must be in error, since some label is clearly observed at the 3-position of the product, as expected for the 1,3-shift which provides the imidoylketene **4** in Scheme 2. Our experiments are therefore in full agreement with the earlier matrix-isolation work.[3,6]

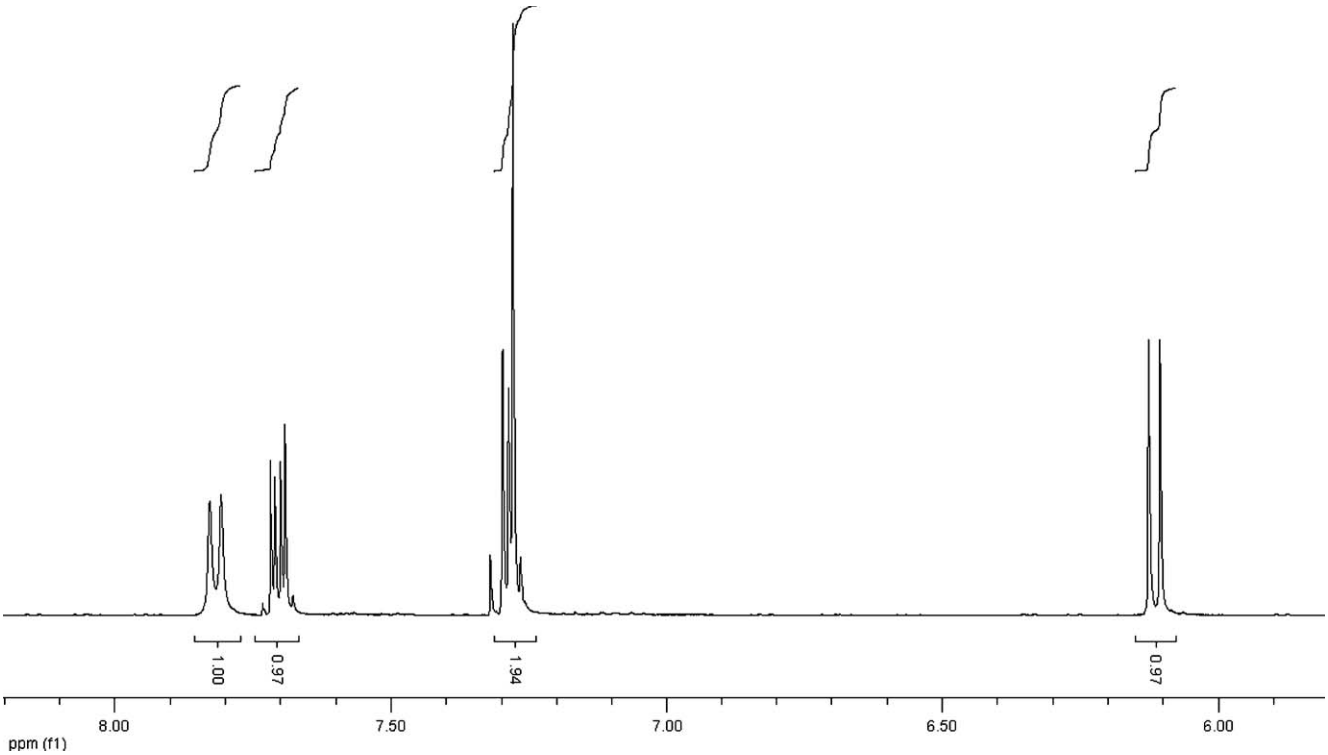


Figure 3 Aromatic region of the ^{1}H NMR spectrum (360 MHz, DMSO-d_6) of the entire pyrolysate from **2d** showing exclusive formation of 8-methoxyquinolin-4-one (**3d**) at 500 °C

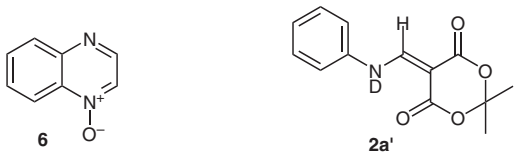


Figure 4

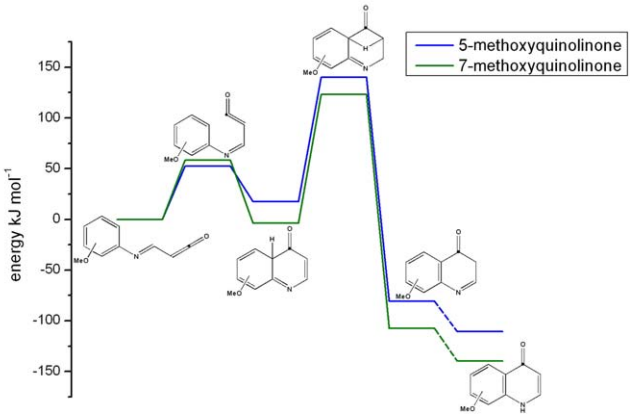


Figure 5 Energy profile for the formation of 5/7-methoxyquinolin-4-one (**3cb** and **3ca**)

With the mechanism of Scheme 2 reasonably established, we have employed DFT calculations (at B3LYP/6-31G** level)[22] which rationalize that the 7-isomers are favored, both kinetically and thermodynamically, from the pyrolysis of both the *m*-methoxy and *m*-cyano compounds **2c** and **2f**, respectively, in agreement with our experimental results (Figure 5, Figure 6). Figures 5 and 6 are in general accord with previous calculations of imidoylketene energy surfaces.[8]

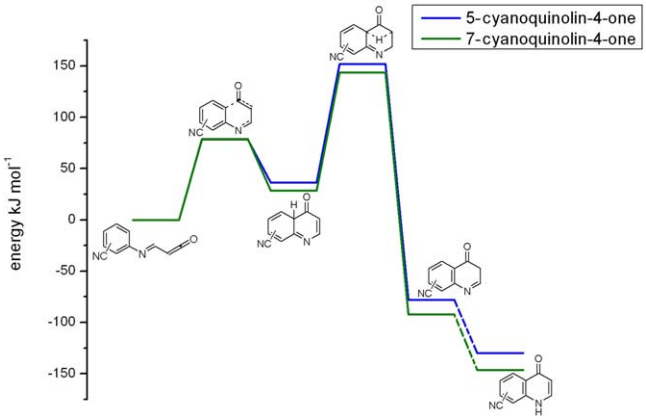


Figure 6 Energy profile for the formation of 5/7-cyanoquinolin-4-one (**3fb** and **3fa**).

According to the previous authors, FVP of the benzimidazole derivative **7** (Figure 7) gave no products due to its involatility.[5] However, in our hands, the pyrolysis cleanly yielded the cyclized product **8**, with a small amount of 2-aminobenzimidazole. Pure 1*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidin-4-one (**8**) could be obtained in 62% yield (300 mg scale) by recrystallization from methanol.[23]

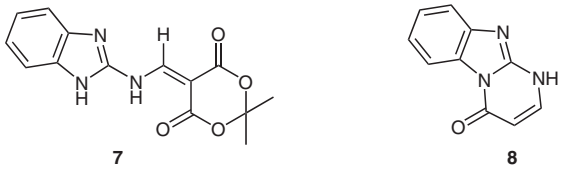


Figure 7

In summary, our investigations of typical reactions reported in ref. 5 have revealed significant discrepancies. First, we have shown that the efficiency of the cyclization to quinolin-4-ones is independent of the electronic nature of the aromatic ring. Second, the results of deuterium-labeling studies have implied the formation of an imidoylketene intermediate, as expected from earlier matrix-isolation work.[3,6] Third, in our hands the preparative yields of quinolin-4-ones under FVP conditions are invariably much higher than the NMR yields reported;[5] the method can be recommended as a synthetic route to quinolin-4-ones which avoids high-boiling solvents. Finally, there is significant regioselectivity in the cyclization of the *m*-substituted compounds, such as **2c** and **2f**, in both cases favoring the less sterically hindered 7-substituted isomer. Further examples of these reactions, including cases which are highly selective for 5-substituted quinolin-4-ones, will be reported in a future paper.

Formation of 2

The appropriate aniline derivative (10 mmol) was added to a soln of methoxymethylene Meldrum's acid **1** (10 mmol) in the minimum volume of MeCN. After 15 min, the solvent was removed to leave the anilinomethylene derivatives **2** in almost quantitative yield.

Preparation of Quinolin-4-ones 3 by FVP

FVP reactions were carried out by sublimation of the precursor **2** under reduced pressure through an empty silica tube (35 × 2.5 cm) heated by an electrical tube furnace. The products were collected at the exit point of the furnace. Upon completion of the pyrolysis the trap was allowed to warm to r.t. under an atmosphere of dry nitrogen. The product was dissolved in DMSO-d_6 for NMR studies or suspended in acetone and recrystallized (preparative studies). Pyrolysis conditions are reported in the form: precursor (quantity), furnace temperature (T_f), inlet temperature (T_i), pressure (P_{range}) and pyrolysis time (t).

FVP of the Labeled Substrate 2a′

The substrate **2a** (0.06 g) was recrystallized from MeOD within the inlet tube of the pyrolysis apparatus. The solvent was removed and the residue was pyrolyzed in the usual way (T_f = 500 °C, T_i = 170 °C, t = 20 min, $P = 2.3 \cdot 10^{-5}$ bar). The ^{1}H NMR spectrum of the product showed ca. 72% deuterium incorporation at the 3-position. The isotopic incorporation is not 100% because of the 1,5-hydrogen shift step[8] (shown in Scheme 2) and because of a possible isotope effect in the final tautomerization.

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(12) FVP of **2b** (0.600 g, T_f = 600 °C, T_i = 170 °C, t = 50 min, $P = 2.3 \cdot 10^{-5}$ bar) gave a yellow solid (0.403 g, quant.), recrystallization from MeOH gave 6-methoxy-1*H*-quinolin-4-one (**3b**, 0.234 g, 61%); mp 243–246 °C (from MeOH; lit.[11] 251–252 °C). ^{1}H NMR (360 MHz, DMSO-d_6): δ = 11.78 (1 H, br s), 7.87 (1 H, d, ^3J = 7.2 Hz), 7.53–7.52 (2 H, m), 7.30 (1 H, dd, ^3J = 9.1 Hz, ^4J = 2.1 Hz), 6.03 (1 H, d, ^3J = 7.2 Hz), 3.85 (3 H, s), see Figure 1.
FVP of **2c** (0.704 g, T_f = 600 °C, T_i = 160 °C, t = 1 h, $P = 1.9 \cdot 10^{-5}$ bar) gave a yellow solid (0.414 g, 93%), in which the ratio **3ca**/**3cb** was 7:93 by ^{1}H NMR spectroscopy, and which provided pure 7-methoxy-1*H*-quinolin-4-one (**3cb**, 0.277 g, 62%), after recrystallization from MeOH, mp 210–212 °C (from MeOH; lit.[11] 219–220 °C). ^{1}H NMR (360 MHz, DMSO-d_6): δ = 11.62 (1 H, br s), 8.00 (1 H, dd, ^3J = 7.6 Hz, ^4J = 2.5 Hz), 7.84 (1 H, d, ^3J = 7.6 Hz), 6.94–6.90 (2 H, m), 5.97 (1 H, d, ^3J = 7.6 Hz), 3.86 (3 H, s), see Figure 2.
FVP of **2d** (0.850 g, T_f = 500 °C, T_i = 160 °C, t = 25 min, $P = 3.6 \cdot 10^{-5}$ bar) gave 8-methoxy-1*H*-quinolin-4-one (**3da**, 0.535 g, 99%); mp 124–126 °C [from EtOH; lit.[13] 134–135 °C(hydrate)]. ^{1}H NMR (360 MHz, DMSO-d_6): δ = 7.82 (1 H, d, ^3J = 7.2 Hz), 7.70 (1 H, dd, ^3J = 6.5 Hz, ^4J = 2.9 Hz), 7.30–7.28 (2 H, m), 6.12 (1 H, d, ^3J = 7.6 Hz), 4.30 (3 H, s), see Figure 3.

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(15) FVP of **2e** (0.610 g, T_f = 600 °C, T_i = 200 °C, t = 1.25 h, $P = 3.1 \cdot 10^{-5}$ bar) gave 6-cyano-1*H*-quinolin-4-one[16] (**3e**) as an orange solid (0.358 g, 94%); mp 186 °C (from MeOH). ^{1}H NMR (250 MHz, DMSO-d_6): δ = 8.47 (1 H, dd, ^4J = 1.9 Hz, ^5J = 0.5 Hz), 8.06 (1 H, d, ^3J = 7.6 Hz), 8.02 (1 H, dd, ^3J = 8.7 Hz, ^4J = 1.9 Hz), 7.72 (1 H, dd, ^3J = 8.7 Hz, ^5J = 0.5 Hz), 6.20 (1 H, d, ^3J = 7.6 Hz).
FVP of **2f** (0.306 g, T_f = 650 °C, T_i = 210 °C, t = 25 min, $P = 4.0 \cdot 10^{-5}$ bar) gave a ca. 25:75 mixture of 5- and 7-cyano-1*H*-quinolin-4-ones[17] (**3fa** and **3fb**; 0.176 g, 94%). ^{1}H NMR (250 MHz, DMSO-d_6): δ (7-isomer, 250 MHz) = 8.28 (1 H, dd, ^3J = 8.3 Hz, ^4J = 0.4 Hz), 8.06 (1 H, m), 7.81 (1 H, m), 7.71 (1 H, dd, ^3J = 8.3 Hz, ^4J = 1.5 Hz), 6.21 (1 H, d, ^3J = 7.5 Hz).
FVP of **2g** (0.604 g, T_f = 600 °C, T_i = 180 °C, t = 20 min, $P = 3.7 \cdot 10^{-5}$ bar) gave 8-cyano-1*H*-quinolin-4-one (**3g**, 0.242 g, 64%); mp 234–236 °C (from MeOH; lit.[18] 260–262 °C). ^{1}H NMR (250 MHz, DMSO-d_6): δ = 8.43 (1 H, dd, ^3J = 8.0 Hz, ^4J = 1.7 Hz), 8.25 (1 H, dd, ^3J = 7.4 Hz, ^4J = 1.7 Hz), 8.00 (1 H, d, ^3J = 7.2 Hz), 7.51 (1 H, dd, ^3J = 8.0, 7.4 Hz), 6.32 (1 H, d, ^3J = 7.2 Hz).

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(20) FVP of **2h** (0.664 g, T_f = 600 °C, T_i = 200 °C, t = 1 h, $P = 3.2 \cdot 10^{-5}$ bar) gave 6-nitro-1*H*-quinolin-4-one (**3h**, 0.283 g, 66%); mp >320 °C (from MeOH; lit.[21] 337–342 °C). ^{1}H NMR (250 MHz, DMSO-d_6): δ = 8.88 (1 H, d, ^3J = 2.8 Hz), 8.46 (1 H, dd, ^3J = 9.2 Hz, ^4J = 2.8 Hz), 8.09 (1 H, d, ^3J = 7.9 Hz), 7.76 (1 H, dd, ^3J = 9.2 Hz, ^5J = 0.5 Hz), 6.24 (1 H, d, ^3J = 7.9 Hz).

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(23) FVP of **7** (0.323 g, T_f = 600 °C, T_i = 200 °C, t = 1 h, $P = 3.3 \cdot 10^{-5}$ bar) gave a yellow solid (0.182 g) and recrystallization from MeOH provided 1*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidin-4-one (**8**, 0.129 g, 62%); mp 285–287 °C (from MeOH; lit.[24] 290 °C). ^{1}H NMR (250 MHz, DMSO-d_6): δ = 8.45 (1 H, d, ^3J = 8.0 Hz), 8.00 (1 H, d, ^3J = 6.9 Hz), 7.58 (1 H, d, ^3J = 7.6 Hz), 7.50 (1 H, td, ^3J = 7.6 Hz, ^4J = 1.3 Hz), 7.34 (1 H, td, ^3J = 8.0 Hz, ^4J = 1.3 Hz), 5.99 (1 H, d, ^3J = 6.9 Hz).

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