Synthesis of Quinolone-Fused Multi-ring-Sized Heterocycles via Combined Claisen Rearrangement/Ring-Closing Metathesis Reactions

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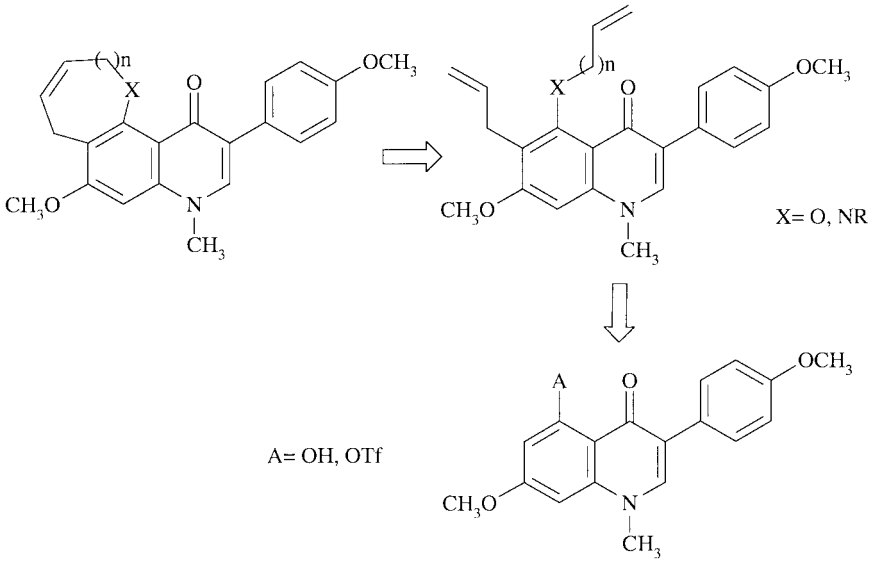
Abstract: Synthetic strategy on 4-quinolone nucleus coupling aza-Claisen rearrangement and ring-closing metathesis was developed. Thus, quinolone-fused multiring-sized oxygen heterocycles **5a**–**c** were prepared from 5-hydroxy-7-methoxy-3-(4-methoxyphenyl)-4(1*H*)-quinolone (**1**). According to the same strategy, azepino[2,3-*f*]quinolone derivative **9** was synthesised from triflate **6**.

Key words: quinolone, Claisen rearrangement, olefin, ring-closing metathesis

The ring-closing metathesis (RCM) reaction has become a versatile method for constructing cyclic alkenes or alkynes.[1] This method has rapidly evolved into a routine tool for the synthesis of natural products,[2] medium-ring and macro-ring carbocyclic or heterocyclic motifs.[3] The generalisation into synthetic organic chemistry has been driven primarily by the discovery of well-defined and functional-group-tolerant catalysts independently by Schrock and Grubbs.[1e]

In our ongoing research of new 4-quinolones with potential antitumor activity,[4] we focused our attention on the synthesis of dihydrooxepino-, oxecino-, oxonino[2,3-*f*]quinolin-11-one or azepino[2,3-*f*]quinolin-11-one compounds. A retrosynthetic analysis shows that oxygen or nitrogen heterocyclic cores can be prepared using a combined aza-Claisen rearrangement/RCM methodology (Scheme 1).[5]

Herein, we report the successful synthesis of new quinolone-fused multiring-sized heterocycles. The RCM oxygen precursors **4** were prepared from 5-hydroxy-7-methoxy-3-(4-methoxyphenyl)-4(1*H*)-quinolone (**1**)[6] as illustrated in Scheme 2. Allylation of **1** in the presence of sodium hydride (2 equivalents) in DMF afforded **2** in 71% optimised yield. It should be noted that compound **4a** was also isolated in 5% yield. Claisen rearrangement[7] of allyl compound **2** in xylene was carried out in a sealed tube at 200 °C for 24 hours. 6-Allyl-5-hydroxy-4-quinolone (**3**) was obtained in 80% yield. Alkylation of **3** in the presence of sodium hydride (2 equivalents) and 3-bromopentene, 4-bromobutene or 5-bromopentene (2 equivalents) in DMF afforded **4a**–**c** in fair yields.



Scheme 1

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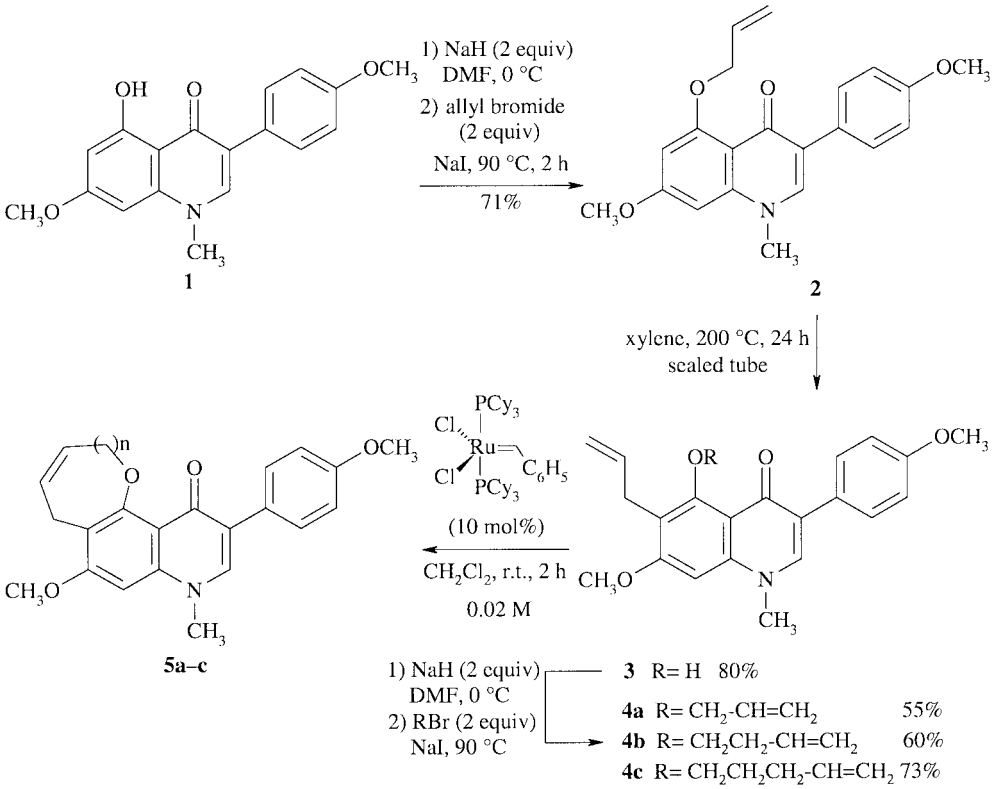

Scheme 2

Table 1 Synthesis of Derivatives **5**

Compd	n	Yield (%)	Mp (°C)
5a	1	81	175–176 (EtOAc)[a]
5b	2	86	200–202 (EtOAc)[a]
5c	3	80	243–244 (EtOAc)[a]

[a] Recrystallisation solvent.

Ring-closing metathesis[7] with commercially available Grubb's catalyst (10 mol%) in dichloromethane (0.02 M) at r.t. converted **4a** to a single isomer of cyclised compound **5a**[8] in 81% yield. The structure was established from ^{1}H NMR coupling constants and 2D NOESY experiments.

Similarly, the same reaction was applied to compounds **4b** and **4c** to give eight- and nine-membered fused ring derivatives **5b** and **5c** in good yields (Table 1).[9] In our hands, no *E*-isomer of cyclised compound was observed. Following these results, we considered the preparation of azepino[2,3-*f*]quinolin-11-one derivative **9** from triflate **6**.[4] As previously reported,[4] an aromatic nucleophilic substitution reaction occurred when **6** was heated in the presence of primary or secondary amine. From this statement, we planned to treat the same triflate with diallylamine to undergo a SN_{Ar} followed by a 3-aza-Claisen rearrangement of the intermediate. The reaction between **6** and diallylamine in a sealed tube at 120 °C for 24 hours afforded the desired compound **7**[10] in 76% optimised yield (Scheme 3). Without the nitrogen protecting group, the ring-closure metathesis of **7** failed.[1c] Compound **7** was acetylated according to classical method. Finally, RCM reaction on **8** afforded seven-membered ring derivative **9**[11] in 95% yield. Again, the structure was determined by NMR experiments.

In summary, we have developed an efficient route to quinolone-fused multiring-sized oxygen heterocycles **5** using combined Claisen rearrangement and ring-closing metathesis reactions. The same approach was performed on 5-triflate **6** to afford azepino[2,3-*f*]quinolin-11-one (**9**).

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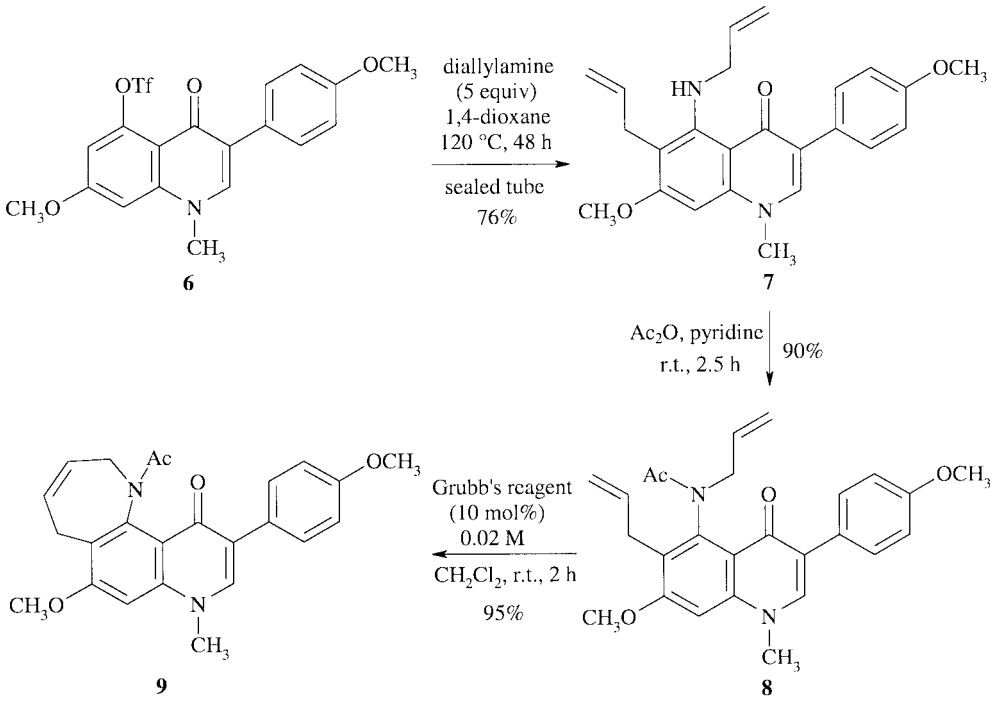

Scheme 3

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(7) **Typical RCM Procedure:** Under argon atmosphere, Grubb's reagent (19.6 mg, 0.02 mmol) was added to a solution of **4a** (93 mg, 0.24 mmol) in dry CH_2Cl_2 (10 mL). The final solution was stirred at r.t. for 2 h. The solvent was evaporated. The residue was purified by column chromatography (petroleum ether–EtOAc, 2:8; then EtOAc) to give 70 mg (81%) of **5a**.

(8) Physical data of compound **5a**: mp 175–176 °C (EtOAc). IR (KBr): ν = 1626, 1609, 1584, 1511 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.52 (d, 2 H, *J* = 8.8 Hz, Ar-H), 7.42 (s, 1 H, =CH), 6.89 (d, 2 H, *J* = 8.8 Hz, Ar-H), 6.36 (s, 1 H, Ar-H), 5.89–5.77 (m, 1 H, CH=), 5.51–5.45 (m, 1 H, CH=), 4.80–4.77 (m, 2 H, CH_2), 3.90 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.69 (s, 3 H, NCH_3), 3.58–3.54 (m, 2 H, CH_2). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 175.6 (CO), 159.7 (C), 158.7 (C), 158.6 (C), 141.6 (C), 140.4 (CH), 130.1 (2 CH), 128.6 (CH), 128.2 (C), 125.7 (CH), 124.4 (C), 123.1 (C), 115.9 (C), 113.7 (2 CH), 91.7 (CH), 70.2 (CH_2), 55.7 (CH_3), 55.4 (CH_3), 41.4 (CH_3), 21.5 (CH_2). MS (IS): *m/z* = 364 ($M + H^+$). Anal. Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 73.03; H, 5.94; N, 3.77.

(9) All new compounds gave satisfactory spectroscopic (^1H-, ^{13}C NMR, MS and IR) and analytical data.

(10) Physical data of compound **7**: mp 119–120 °C (EtOAc). IR (KBr): ν = 3460, 1630, 1610, 1570, 1560, 1512 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 10.18 (broad s, 1 H, NH), 7.49 (d, 2 H, *J* = 7.8 Hz, Ar-H), 7.43 (s, 1 H, =CH), 6.93 (d, 2 H, *J* = 7.8 Hz, Ar-H), 6.06 (s, 1 H, Ar-H), 6.17–5.89 (m, 2 H, =CH), 5.34–5.25 (m, 1 H, $=CH_2$), 5.08–4.95 (m, 3 H, $=CH_2$), 3.90–3.82 (m, 5 H, $OCH_3 + CH_2$), 3.79 (s, 3 H, OCH_3), 3.61 (s, 3 H, NCH_3), 3.44–3.42 (m, 2 H, CH_2). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 178.7 (CO), 162.0 (C), 158.6 (C), 154.9 (C), 142.1 (C), 140.2 (C), 137.9 (C), 137.2 (C), 130.1 (2 CH), 128.1 (CH), 121.8 (CH), 115.1 (CH_2), 114.4 (CH_2), 113.6 (2 CH), 112.0 (CH), 110.7 (C), 86.1 (CH), 55.4 (CH_3), 55.3 (CH_3), 51.4 (CH_2), 41.5 (CH_3), 30.2 (CH_2). MS (IS): *m/z* = 391 ($M + H^+$). Anal. Calcd for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71; N, 7.17. Found: C, 73.95; H, 6.60; N, 7.08.

(11) Physical data of compound **9**: mp 245–246 °C (EtOAc). IR (KBr): ν = 1671, 1635, 1612, 1575, 1513 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.54 (s, 1 H, =CH), 7.50 (d, 2 H, *J* = 8.7 Hz, Ar-H), 6.88 (d, 2 H, *J* = 8.7 Hz, Ar-H), 6.69 (s, 1 H, Ar-H), 5.75–5.68 (m, 1 H, =CH), 5.52–5.40 (m, 2 H, CH_2 + =CH), 3.98 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.78 (s, 3 H, NCH_3), 3.63–3.43 (m, 3 H, CH_2), 1.74 (s, 3 H, $COCH_3$). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 174.9 (CO), 169.5 (CO), 158.9 (C), 158.6 (C), 142.9 (C), 141.8 (C), 140.8 (CH), 130.1 (2 CH), 128.2 (C+CH), 127.7 (C), 124.2 (CH), 123.3 (C), 117.0 (C), 113.8 (2 CH), 95.6 (CH), 56.0 (CH_3), 55.4 (CH_3), 43.6 (CH_2), 41.6 (CH_3), 21.8 (CH_3), 21.5 (CH_2). MS (IS): *m/z* = 405 ($M + H^+$). Anal. Calcd for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93. Found: C, 70.99; H, 6.12; N, 6.89.