Ring-Closing Metathesis as a Key Step in the Synthesis of 2-Pyridones and Pyridine Triflates

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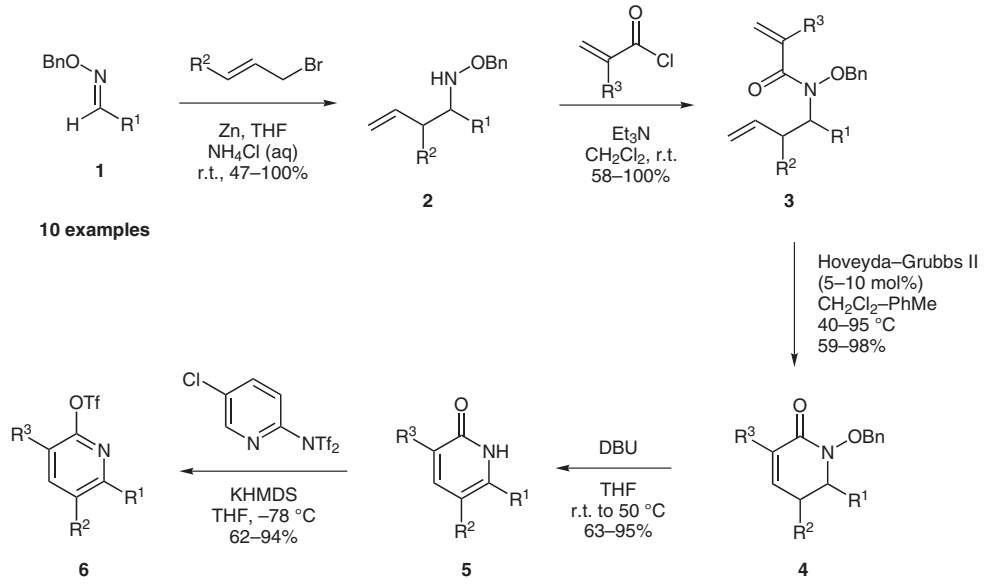
Abstract: The ring-closing metathesis transformation has been employed to construct a library of functionalized 2-pyridones and pyridine triflates. Using this mild approach, a range of substituent patterns can be built into the aromatic core, including groups which can be demanding to incorporate using alternative protocols.

Key words: ring-closing metathesis, elimination, 2-pyridone, pyridine, triflation



Scheme 1 Preparation of 2-pyridones and pyridines

Ruthenium-catalyzed ring-closing metathesis (RCM) has recently emerged as a powerful tool for the synthesis of aromatic heterocycles and carbocycles.[1] The relatively mild conditions of the RCM transformation allow the incorporation of a wide range of functional groups, which presents a flexible method for *de novo* syntheses of aromatic motifs.

This approach has recently been employed to construct a library of functionalized 2-pyridones (Scheme 1).[1g] The heterocyclic core of **5** was constructed by RCM of acrylamide **3**, which was equipped with a leaving group (OBn) on nitrogen. Following cyclization, the elimination of benzyl alcohol was carried out using DBU to provide the desired 2-pyridone **5** in excellent yield. Using this flexible procedure, it was possible to incorporate an array of substituents at R^1 (including methyl ester, 2-pyridinyl, 2-quinolinyl, 2-quinoxalinyl), R^2 (methyl, phenyl), and R^3 (methyl, trifluoromethyl). In addition, 2-pyridones **5** could be manipulated further by bromination at C-3 or C-5. Futhermore, their efficient conversion into pyridine triflates **6** was achieved using the protocol developed by Comins et al.;[2] such intermediates can be functionalized using a variety of coupling procedures.[3]

The synthesis of substituted 2-pyridones and pyridines is of importance due to the abundance of these motifs in natural products, pharmaceutical drugs, agrochemicals, and coordination chemistry.[4] Therefore, we have utilized this procedure to produce significant quantities of 2-pyridone **11** (Scheme 2). RCM precursor **9** was synthesized from

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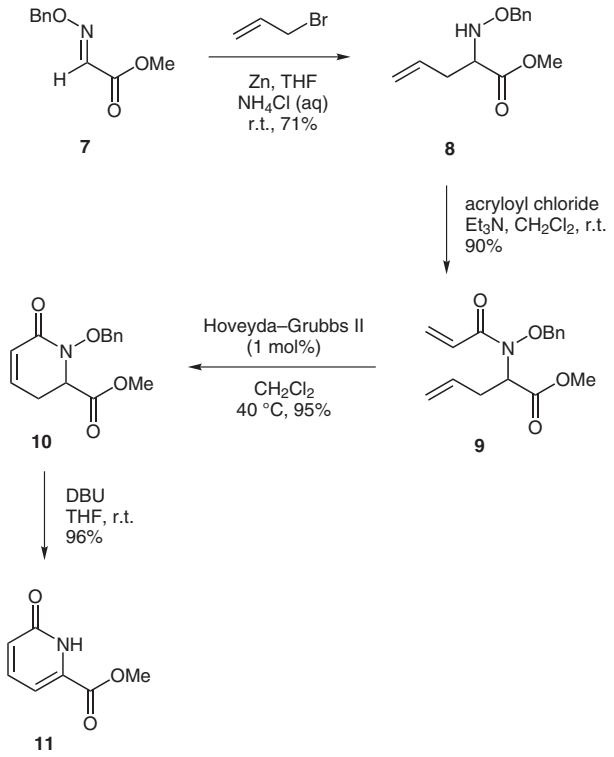
oxime ether **7** in two steps and 64% yield. The key cyclization was carried out with 1 mol% Hoveyda–Grubbs second-generation catalyst at 40 °C, which provided the dihydropyridone **10** in 95% yield after 18 hours. The desired 2-pyridone **11** was obtained upon treatment of **10** with DBU in THF at room temperature. Thus, the overall yield of aromatic **11** from oxime ether **7** was 58%.



Scheme 2 Preparation of methyl 6-oxo-1,6-dihydropyridine-2-carboxylate (**11**)

In conclusion, we have developed an efficient and flexible route to a variety of functionalized 2-pyridones and pyridines. Using this approach, a range of substitution patterns can be built into the aromatic core and groups (e.g., CF_3), which can be demanding to incorporate with other procedures.

THF was purified by filtration through two columns of activated alumina (grade DD-2) as supplied by Alcoa, employing the method of Grubbs et al.[5] CH_2Cl_2 was purified by filtration through two columns of basic activated alumina (Brockman I, standard grade, ~150 mesh, 58 Å) as supplied by Aldrich. Et_3N was purified by distillation over CaH_2, and stored over CaH_2. TLC was performed on Merck Kieselgel 60 F_{254} 0.25 mm precoated aluminum backed silica plates. Flash column chromatography was carried out using Merck Kieselgel 60 (40–63 μm). ^{1}H NMR spectra were recorded on a Bruker Avance AV 400 (400 MHz) spectrometer. ^{13}C NMR spectra were recorded on the same spectrometer at 100 MHz. IR spectra were recorded on a Bruker Tensor 27 Ft-IR spectrometer. Mass spectra (ESI) were recorded on a Fisons Platform II. Accurate mass (HRMS) data were recorded under conditions of ESI on a Micromass LCT (resolution = 5000 FWHM) or a Bruker MicroToF spectrometer (resolution = 10000 FWHM). Melting points were obtained using a Leica VMTG heated-stage microscope. Oxime ether **7** was prepared according to literature procedures.[6] Petroleum ether (PE) used refers to the fraction boiling in the range 40–60 °C.

Methyl 2-(Benzyloxyamino)pent-4-enoate (8)[6b]

A 100 mL round bottom flask containing oxime ether **7** (1.50 g, 7.77 mmol) was charged with THF (6.5 mL) and sat. aq NH_4Cl (33.5 mL). Zn dust (1.12 g, 17.1 mmol) was added and the suspension was stirred at r.t. Allyl bromide (1.21 mL, 14.0 mmol) was then added dropwise over 5 min, whereupon an exotherm was observed. The suspension was stirred for a further 30 min at r.t. before transferring to a separating funnel and extracting with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The remaining colorless oil was purified by flash column chromatography (12 cm × 4 cm, 9:1 PE–EtOAc) to give **8** as a colorless oil (1.30 g, 71%).

IR (film): 3264, 3032, 2953, 1743, 1642, 1496, 1436, 1365, 1202, 993, 913, 743 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32–2.37 (2 H, m), 3.70 (1 H, t, *J* = 7.0 Hz), 3.75 (3 H, s), 4.72 (2 H, s), 5.06–5.13 (2 H, m), 5.73 (1 H, ddt, *J* = 17.0, 10.5, 7.0 Hz), 5.96 (1 H, br s), 7.27–7.36 (5 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.9, 52.0, 63.3, 76.2, 118.2, 127.8, 128.3, 128.5, 133.0, 137.6, 173.6.

Methyl 2-[*N*-(Benzyloxy)acrylamido]pent-4-enoate (9)

A 50 mL round-bottomed flask containing amine **8** (1.30 g, 5.53 mmol) was purged with argon before charging with CH_2Cl_2 (20 mL). Et_3N (1.54 mL, 11.1 mmol) was added to the stirred solution at r.t. before cooling to 0 °C. Acryloyl chloride (674 μL, 8.30 mmol) was added dropwise over 5 min at 0 °C, during which time the solution turned yellow. The solution was then warmed to r.t. and stirred for a further 10 min. The dark orange mixture was then transferred to a separating funnel and washed with 1.0 M aq HCl (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The remaining orange oil was purified by flash column chromatography (12 cm × 4 cm, 8:1 PE–EtOAc) to give **9** as a very pale yellow oil (1.44 g, 90%).

IR (film): 2952, 1746, 1665, 1620, 1410, 1229, 986, 920, 787, 744, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.75–2.89 (2 H, m), 3.77 (3 H, s), 4.93 (1 H, d, *J* = 10.5 Hz), 5.02 (1 H, d, *J* = 10.5 Hz), 5.04–5.07 (1 H, m), 5.11 (1 H, dd, *J* = 10.5, 1.0 Hz), 5.18 (1 H, dd, *J* = 17.0, 1.0 Hz), 5.78 (1 H, dd, *J* = 10.5, 2.0 Hz), 5.82 (1 H, ddt, *J* = 17.0, 10.5, 7.0 Hz), 6.45 (1 H, dd, *J* = 17.0, 2.0 Hz), 6.73 (1 H, dd, *J* = 17.0, 10.5 Hz), 7.38–7.41 (5 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.6, 52.5, 60.7, 79.0, 118.4, 126.0, 128.7, 129.0, 129.0, 130.2, 133.6, 134.3, 168.3, 170.3.

MS (ESI): *m*/*z* (%) = 312 (100, MNa^+), 290 (30, MH^+), 236 (10), 218 (10).

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{19}NO_4Na$ (MNa^+): 312.1206; found: 312.1207 (–0.18 ppm).

Methyl 1-(Benzyloxy)-6-oxo-1,2,3,6-tetrahydropyridine-2-carboxylate (10)

A 250 mL round-bottomed flask fitted with a condenser and containing acrylamide **9** (1.44 g, 4.98 mmol) was purged with argon before charging with CH_2Cl_2 (200 mL). Hoveyda–Grubbs second-generation catalyst (31 mg, 0.05 mmol) was added and the green solution was heated at reflux for 18 h, during which time the solution became golden brown in color. The solvent was removed under reduced pressure and the remaining brown oil was purified by flash column chromatography (12 cm × 4 cm, 2:1 PE–EtOAc) to give **10**

as a very light brown oil (1.24 g, 95%), which partially solidified upon standing.

IR (film): 2954, 1750, 1692, 1389, 1210, 1080, 998, 809, 757, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.62–2.66 (2 H, m), 3.73 (3 H, s), 3.94–3.98 (1 H, m), 4.96 (1 H, d, *J* = 11.0 Hz), 5.04 (1 H, d, *J* = 11.0 Hz), 5.94 (1 H, ddd, *J* = 10.0, 2.0, 1.0 Hz), 6.34–6.46 (1 H, m), 7.35–7.46 (5 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.4, 52.8, 62.3, 77.4, 125.3, 128.5, 128.8, 129.8, 135.6, 137.1, 165.1, 170.8.

MS (ESI): *m*/*z* (%) = 284 (100, MNa^+), 262 (100, MH^+).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{15}NO_4Na$ (MNa^+): 284.0893; found: 284.0894 (–0.14 ppm).

Methyl 6-Oxo-1,6-dihydropyridine-2-carboxylate (11)

A 50 mL round-bottomed flask containing dihydropyridone **10** (1.24 g, 4.75 mmol) was purged with argon before charging with THF (30 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (4.97 mL, 33.3 mmol) was added dropwise and stirring was continued at r.t. for 1.75 h, during which time the solution became yellow in color. The mixture transferred directly to the column, then purified by flash column chromatography (12 cm × 4 cm, EtOAc → 10:1 EtOAc–MeOH) to give **11** as a colorless solid (699 mg, 96%); mp 100–103 °C.

IR (film): 3305, 1725, 1661, 1613, 1543, 1440, 1352, 1308, 1194, 1132, 1062, 1005, 891 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.94 (3 H, s), 6.83 (1 H, dd, *J* = 9.5, 1.0 Hz), 6.97 (1 H, dd, *J* = 7.0, 1.0 Hz), 7.45 (1 H, dd, *J* = 9.5, 7.0 Hz), 11.28 (1 H, br s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.3, 109.6, 126.9, 133.9, 139.7, 161.4, 163.1.

MS (ESI): *m*/*z* = 176 (100%, MNa^+).

HRMS (ESI): *m*/*z* calcd for $C_7H_7NO_3Na$ (MNa^+): 176.0318; found: 176.0318 (–0.73 ppm).

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