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Synthesis of alkyl *N*-(4-nitrophenyl)-3/2-oxomorpholine-2/3-carboxylates by rhodium(II) acetate catalyzed O–H and N–H carbene insertion

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ABSTRACT

The synthesis of methyl *N*-(4-nitrophenyl)-3-oxomorpholine-2-carboxylate and ethyl *N*-(4-nitrophenyl)-2-oxomorpholine-3-carboxylate, via rhodium(II) acetate catalyzed intermolecular O–H and intramolecular N–H carbene insertion, is described. The products represent new and versatile building blocks for the synthesis of bioactive compounds of pharmaceutical interest.

The morpholin-3-one (**1**) and morpholin-2-one (**2**) skeletons and their derivatives are important synthons for the preparation of bioactive compounds.[1] In the course of our medicinal chemistry program, aimed at producing dual antithrombotic compounds with highly overlapping factor Xa inhibitor and fibrinogen receptor antagonist pharmacophores,[2] protected isomeric 4-(4-nitrophenyl)-3-oxomorpholine-2-carboxylate **3** and 4-(4-nitrophenyl)-2-oxomorpholine-3-carboxylate **4** (Fig. 1) were required as key intermediates in order to functionalize the parent morpholin-3-one moiety of the lead compound with a negatively charged carboxylate group (Fig. 2). 2,4-Disubstituted morpholin-3-ones and 3,4-disubstituted morpholin-2-ones are generally prepared by either one- or two-bond cyclization reactions[1,3–7] or by direct functionalization of N-substituted morpholin-2/3-ones with electrophilic reagents at the 2- or 3-position.[8–13]

Ethyl 3-oxo-4-phenylmorpholine-2-carboxylate (**5**),[14] which closely resembles 3-oxo-morpholine-2-carboxylate **3**, is the only known 4-phenylmorpholin-3-one derivative bearing a protected carboxylate group. Compound **5** was prepared by rhodium(II) acetate catalyzed intramolecular O–H insertion of the carbenoid intermediate obtained by decomposition of diazo-*N*-(2-hydroxyethyl)-*N*-phenylmalonamide ethyl ester.[14] No isomeric 2-oxomorpholine-3-carboxylate resembling **4** is known in the literature, and an attempt to prepare structurally related ethyl *N*-benzyloxycarbonyl-2-oxomorpholine-3-carboxylate (**6**) via an $Rh_2(OAc)_4$-catalyzed N–H insertion reaction failed.[15]

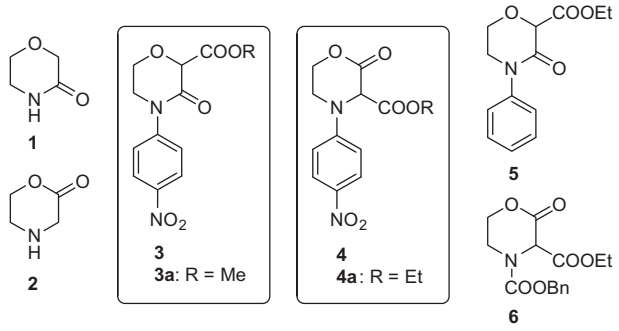

Figure 1. Envisaged 3/2-oxomorpholine-2/3-carboxylates **3a** and **4a** and related compounds.

We report herein the rhodium(II) acetate catalyzed syntheses of isomeric methyl 4-(4-nitrophenyl)-3-oxomorpholine-2-carboxylate (**3a**) and ethyl 4-(4-nitrophenyl)-2-oxomorpholine-3-carboxylate (**4a**) (Fig. 1), which are versatile new building blocks for the synthesis of bioactive compounds of pharmaceutical interest. They can be functionalized easily at the aromatic nitro group, and they are key intermediates in the synthesis of factor Xa-inhibitor rivaroxaban analogues with potential dual antithrombotic activity.[2]

Although 3-oxomorpholine-2-carboxylates **3** and **5** differ solely in the *p*-nitro substituent on the phenyl ring, direct transfer of the methodology for synthesizing **5**, which comprises O1–C2 bond formation by intramolecular insertion of a carbene generated from α-diazoester **7** into the O–H bond of the *N*-(2-hydroxyethyl) moiety (Fig. 3),[14] proved to be unsuccessful in our hands for preparing **3**.[16]

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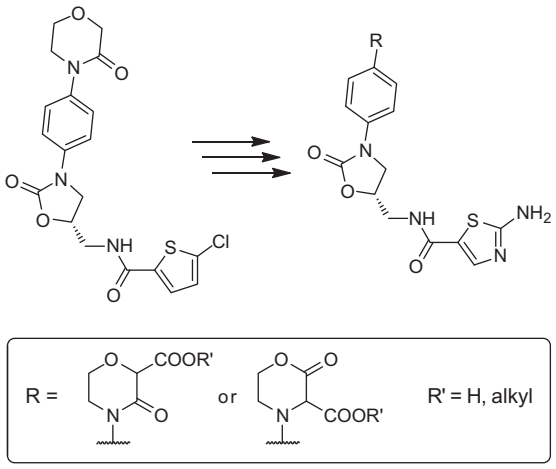


Figure 2. Evolution of dual antithrombotic compounds requesting development of synthesis of **3** and **4**.

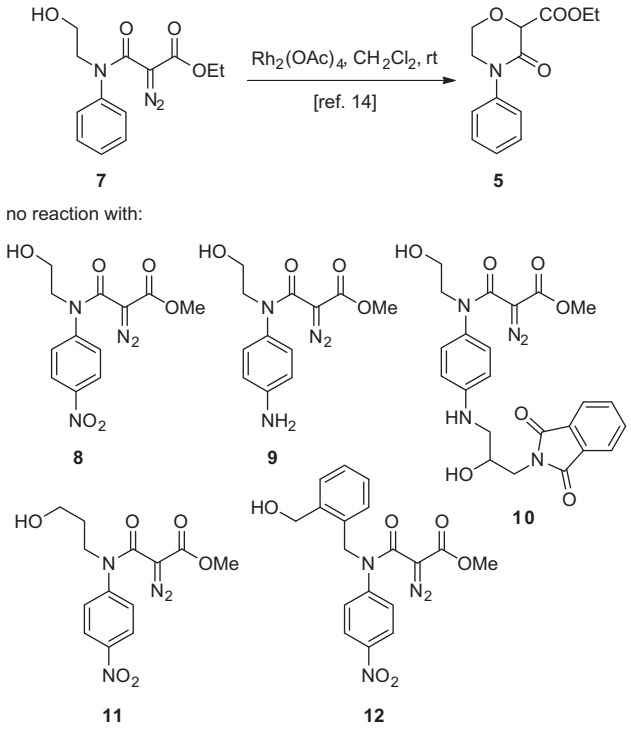
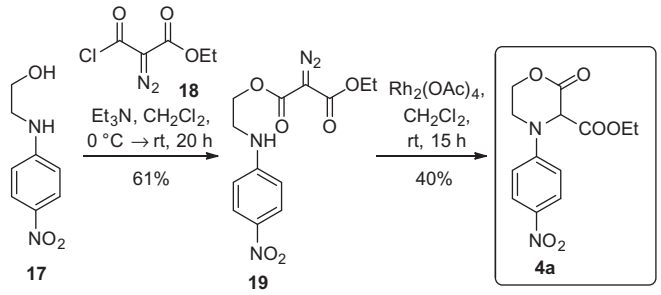


Figure 3. Attempted intramolecular carbene insertion into the O-H bond.

When **8** was treated with rhodium(II) acetate in dichloromethane, benzene, tetrahydrofuran or water at room temperature, or with heating, intramolecular carbene insertion into the O–H bond did not take place. Moreover, the reduced derivative **9**, the corresponding phthalimido protected derivative **10**, the homologous methyl 2-diazo-3-[(3-hydroxypropyl)(4-nitrophenyl)amino]-3-oxopropanoate (**11**), and methyl 2-diazo-3-{[2-(hydroxymethyl)benzyl](4-nitro-phenyl)amino}-3-oxopropanoate (**12**) could not be cyclized by rhodium(II) acetate promoted intramolecular carbene insertion into the O–H bond. This suggests that the synthetic strategy used for preparing **5**[14] (Fig. 3, top) is not generally applicable to the synthesis of *N*-aryl-3-oxomorpholine-2-carboxylates.

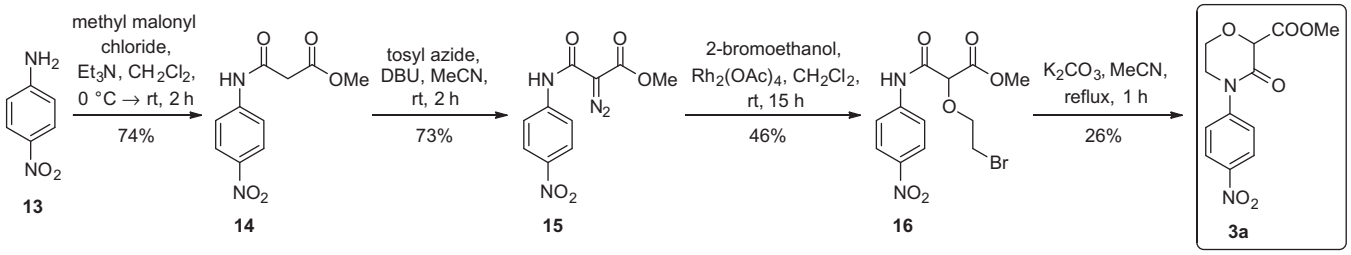


Scheme 2. Synthesis of ethyl 4-(4-nitrophenyl)-2-oxomorpholine-3-carboxylate (**4a**).

Therefore, we explored alternative methods for the synthesis of **3** and found that intermolecular insertion of a carbene, which was generated by decomposition of α-diazomalonate **15**, into the O–H bond of 2-bromoethanol, prior to the cyclization step, enabled successful synthesis of **3a** from 4-nitroaniline (**13**) (Scheme 1). Thus, methyl 3-[(4-nitrophenyl)amino]-3-oxopropanoate (**14**), which was prepared by acylation of 4-nitroaniline with ethyl malonyl chloride, was subjected to a diazo-transfer reaction using tosyl azide in the presence of 1,8- diazabicycloundec-7-ene (DBU) to give methyl 2-diazo-3-[(4-nitrophenyl)amino]-3-oxopropanoate (**15**), which afforded methyl 2-(2-bromoethoxy)-3-[(4-nitrophenyl)amino]-3-oxopro-panoate (**16**)[17] on stirring with 2-bromoethanol in the presence of rhodium(II) acetate at room temperature. Finally, **16** gave methyl 4-(4-nitrophenyl)-3-oxomorpholine-2-carboxylate (**3a**)[18] via intramolecular nucleophilic substitution.

In an attempt to access isomeric 4-(4-nitrophenyl)-2-oxomorpholine-3-carboxylate **4**, we combined our earlier observation that O-acylation of 2-[(4-nitrophenyl)amino]ethanol (**17**) is preferred over N-acylation, with expected rhodium(II)-catalyzed N–H insertion of a carbene generated from α-diazomalonate **19**. Thus, O-acylation of **17** with ethyl 3-chloro-2-diazo-3-oxopropanoate (**18**)[14] in the presence of triethylamine gave 1-ethyl 3-{2-[(4-nitrophenyl)amino]ethyl}-2-diazomalonate (**19**), which afforded **4a** via rhodium(II) acetate catalyzed intramolecular N–H carbene insertion (Scheme 2).[19]

We did not study the reaction scope with different substituents on the morpholinone and phenyl rings because the *p*-nitro group was indispensable for synthetic elaboration of **3** and **4** toward



Scheme 1. Synthesis of methyl 4-(4-nitrophenyl)-3-oxomorpholine-2-carboxylate (**3a**).

potential dual antithrombotic compounds, and because the presence of other substituents on both rings was expected to decrease factor Xa-inhibitory and fibrinogen receptor antagonistic activity. Alternative rhodium ligands were not studied because it is known that some of them, for example, with a perfluorocarboxamide, promote aromatic C–H insertion.[14]

In conclusion, we have developed successful strategies for the rhodium(II) acetate catalyzed preparation of methyl 4-(4-nitrophenyl)-3-oxomorpholine-2-carboxylate (**3a**) starting from 4-nitroaniline, and ethyl 4-(4-nitrophenyl)-2-oxomorpholine-3-carboxylate (**4a**) starting from 2-[(4-nitrophenyl)amino]ethanol. Both compounds can serve as versatile new building blocks for the synthesis of bioactive compounds of pharmaceutical interest.

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Supplementary data

Supplementary data (NMR spectra of compounds **3a**, **4a**, **15**, **16** and **19**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.049.

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16. Compound **3** could not be obtained by nitration of **5**. Attempts to prepare **3** by introduction of an ethoxycarbonyl group at position 2 of 4-(4-nitrophenyl)morpholin-3-one using ethyl chloroformate or diethyl carbonate with lithium diisopropylamide, sodium hydride, or sodium ethoxide as the base, were not successful.
17. Methyl 2-(2-bromoethoxy)-3-[(4-nitrophenyl)amino]-3-oxopropanoate (**16**). Methyl 2-diazo-3-[(4-nitrophenyl)amino]-3-oxopropanoate (**15**) (1.68 g, 6.35 mmol) and 2-bromoethanol (447 μL, 6.35 mmol) were dissolved in dichloromethane (100 mL). $Rh_2(OAc)_4$ (7 mol %) was added and the reaction mixture was stirred at room temperature for 15 h. After removal of undissolved $Rh_2(OAc)_4$, solvent was evaporated under reduced pressure. Residue was purified by flash column chromatography using EtOAc/hexane (1:2) as eluant to afford **16**. Yield: 1.05 g (46%); pale yellow crystals, mp 128–133 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.68 (t, 2H, J = 5.8 Hz, CH_2Br), 3.74 (s, 3H, CH_3), 3.97 (t, 2H, J = 5.8 Hz, OCH_2), 4.90 (s, 1H, CH), 7.92 (d, 2H, J = 9.3 Hz, Ar-H^2,H^6), 8.25 (d, 2H, J = 9.3 Hz, Ar-H^3,H^5), 10.73 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 31.37 (*C*H$_2$Br), 52.53 (CH$_3$), 70.51 (OCH$_2$), 79.66 (CH), 119.65 (Ar-C^{2,6}), 124.92 (Ar-C^{3,5}), 142.88 and 144.05 (Ar-C^{1,4}), 165.04 (NCO), 167.26 (COO). MS (EI) m/z (%): 363.0 ([M+H]$^+$, 92) for ^{81}Br, 361.0 ([M+H]$^+$, 100) for ^{79}Br. HRMS (ESI) calcd for $C_{12}H_{14}BrN_2O_6$ 361.0035, found 361.0045. IR (ATR) 3295, 3108, 1744, 1696, 1618, 1596, 1559, 1507, 1437, 1410, 1377, 1344, 1293, 1255, 1231, 1169, 1109, 1065, 978, 941, 918, 857, 841, 774, 749, 688, 628, 610, 567 cm^{-1}.
18. Methyl 4-(4-nitrophenyl)-3-oxomorpholine-2-carboxylate (**3a**). Methyl 2-(2-bromoethoxy)-3-[(4-nitrophenyl)amino]-3-oxopropanoate (**16**) (964 mg, 2.67 mmol) was dissolved in acetonitrile (30 mL). K_2CO_3 (368 mg, 2.67 mmol) was added and the resulting suspension refluxed for 2 h. After solvent removal, residue was dissolved in dichloromethane (60 mL) and washed with water (2 × 30 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using dichloromethane/EtOAc (19:1) as eluant, yielding **3a**. According to TLC prolongation of reaction time at reflux did not give **3a**. Yield: 195 mg (26%); yellow crystals, mp 132–135 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.75 (s, 3H, CH_3), 3.92–3.95 (m, 2H, OCH_2), 4.08–4.13 (m, 1H, NCH_2), 4.21–4.26 (m, 1H, NCH_2), 5.07 (s, 1H, CH), 7.75 (d, 2H, J = 9.2 Hz, Ar-H^2,H^6), 8.30 (d, 2H, J = 9.2 Hz, Ar-H^3,H^5). ^{13}C NMR (100 MHz, DMSO-d_6) δ 48.23 (OCH$_2$), 52.60 (CH$_3$), 61.99 (NCH$_2$), 76.58 (CH), 124.22 (Ar-C^{3,5}), 125.25 (Ar-C^{2,6}), 144.78 and 146.78 (Ar-C^{1,4}), 163.07 (NCO), 167.56 (COO). MS (EI) m/z (%): 281.1 ([M+H]$^+$, 100). HRMS (ESI) calcd for $C_{12}H_{13}N_2O_6$ 281.0774, found 281.0775. IR (ATR) 3111, 2957, 1743, 1660, 1607, 1590, 1513, 1490, 1472, 1432, 1377, 1343, 1319, 1291, 1255, 1225, 1201, 1151, 1126, 1103, 1032, 984, 968, 938, 856, 815, 752, 700, 606, 534 cm^{-1}.
19. Ethyl 4-(4-nitrophenyl)-2-oxomorpholine-3-carboxylate (**4a**). To a stirred solution of 1-ethyl 3-{2-[(4-nitrophenyl)amino]ethyl} 2-diazomalonate (**19**) (0.97 g, 3 mmol) in dichloromethane (30 mL) $Rh_2(OAc)_4$ (7 mol %) was added and reaction mixture was stirred for 4 days at room temperature. Solvent was evaporated under reduced pressure and residue purified by flash column chromatography using EtOAc/hexane (2:1) as eluant to afford **4a**. Yield: 354 mg (40%); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, 3H, J = 7.2 Hz, CH$_2$CH_3), 3.75–3.80 (m, 2H, NCH_2), 4.36 (ddd, 2H, J = 14.3 Hz, 7.1 Hz, 2.1 Hz, CH_2CH$_3$), 4.59–4.77 (m, 2H, CH_2O), 5.19 (s, 1H, CH), 6.73 (d, 2H, J = 9.4 Hz, Ar-H^2,H^6), 8.20 (d, 2H, J = 9.5 Hz, Ar-H^3,H^5). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.04 (*C*H$_3$), 42.82 (NCH$_2$), 62.33 (*C*H), 63.64 (*C*H$_2$CH$_3$), 65.09 (*C*H$_2$O), 111.20 (Ar-C^{2,6}), 126.05 (Ar-C^{3,5}), 139.63 (Ar-C^4), 150.98 (Ar-C^1), 163.04 (CH$_2$CH$_2$OCO), 166.56 (COO). MS (EI) m/z (%): 295.1 ([M+H]$^+$, 100), 279.1 (40), 165.1 (42). HRMS (ESI) calcd for $C_{13}H_{15}N_2O_6$ 295.0930, found 295.0941. IR (ATR) 3380, 2922, 1751, 1594, 1497, 1465, 1376, 1322, 1277, 1227, 1194, 1110, 1065, 1015, 980, 944, 831, 752, 712, 693, 655, 629, 579 cm^{-1}.