Efficient Proline-Catalyzed Michael-Additions of Unmodified Ketones to Nitroolefins

Supporting Information

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General Experimental Procedure:

A suspension of D- or L- proline (17 mg, 15 mol%) and the nitroolefin (1 mmol) in 8 mL of DMSO and 2 mL of the ketone (10 mmol in the case of tetrahydro-thiopyran-4-one) were stirred at room temperature for 2 – 24 hours. Ethyl acetate (10 mL) and saturated NH_4Cl solution (10 mL) was added and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate mixtures) furnished γ-nitroketones **1** - **7**. Compounds **1**[1], **2**[2], **3**[3], **5**[4], and **8**[5] are known.

(*syn*)-3-Methyl-5-nitro-4-phenyl-pentan-2-one (**2**): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.4 – 7.1 (m, 5H), 4.62 (dd, *J* = 4.8 and 1.8 Hz, 2H), 3.72 – 3.60 (m, 1H), 3.2 – 2.82 (m, 1H), 2.2 (s, 3H), 0.95 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 204.9, 135.0, 130.0, 127.9, 78.4, 49.5, 49.0, 39.1, 15.9. HRMS calcd for $C_{12}H_{15}NO_3$: 221.1052, found: MH^+ = 222. 1125

3-(2-Nitro-1-phenyl-ethyl)-tetrahydro-thiopyran-4-one (**4**): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.37 – 7.14 (m, 5H), 4.72 (dd, *J* = 12.5 and 4.5 Hz, 1H), 4.6 (dd, *J* = 12.5 and 10.0 Hz, 1H), 3.99 (ddd, *J* = 15.4, 10.6 and 4.8 Hz, 1H), 3.09 – 3.01 (m, 1H), 3.0 – 2.9 (m, 2H), 2.85 – 2.75 (m, 2H), 2.59 (dd, *J* = 13.5 and 4.8 Hz, 1H), 2.42 (dd, *J* = 13.5 and 9.5 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 209.5, 136.4, 129.3, 128.1, 78.6, 54.9, 44.5, 35.1, 31.6, 30.9. HRMS calcd for $C_{13}H_{15}NO_3S$: 265.0773, found: MH^+ = 266.0845.

5-Methyl-4-nitromethyl-hexan-2-one (**6**): ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.39 (d, *J* = 5.0 Hz, 2H), 2.6-2.4 (m, 2H), 2.11 (s, 3H), 1.6-1.45 (m, 1H), 1.18 (ddd, *J* = 10.0, 7.1 and 2.0 Hz, 2H), 0.85 (dd, *J* = 2 x 8.5 Hz, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 206.7, 78.4, 44.6, 40.4, 30.8, 30.4, 25.0, 22.3. HRMS calcd for $C_8H_{15}NO_3$: 173.1052, found: MH^+ = 174.1125

7-Methyl-4-nitromethyl-oct-5-en-2-one (**7**): ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.57 (dd, *J* = 14.5 and 7.5 Hz, 1H), 5.23 (dd, *J* = 14.5 and 7.5 Hz, 1H), 4.5 – 4.3 (m, 2H), 3.3 – 3.19 (m, 1H), 2.58 (d, *J* = 6.5 Hz, 2H), 2.28 – 2.15 (m, 1H), 2.1 (s, 3H), 0.9 (d, *J* = 7.0 Hz, 6H).^{13}C NMR (63 MHz, $CDCl_3$) δ 22.2, 30.5, 30.9, 36.7, 45.1, 48.4, 79.0, 123.6, 141.9, 213.4.HRMS calcd for $C_{10}H_{17}NO_3$: 199.1208, found: MH^+ = 200.1272.

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Chiral-Phase HPLC -Data

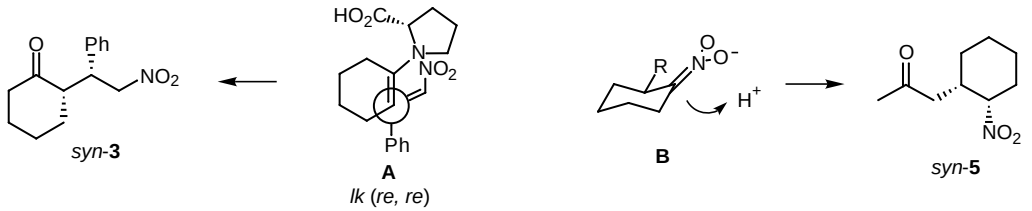
γ-Nitroketone	Daicel Chiralpak
1	AS 15% *i*-PrOH/hexanes, 256nm, 1 mL/min t_R = 17.4 min, 22.4 min
2	AD-RH 28% CH_3CN/H_2O (0.1% TFA), 254nm, 0.5 mL/min t_R = 33.6 min, 36.3 min
3	AS 23% *i*-PrOH/hexanes, 256nm, 1 mL/min t_R = 7.0 min, 9.1 min
4	AS 50% *i*-PrOH/hexanes, 247nm, 0.5mL/min t_R = 25.0 min, 32.4 min
5	AS 3% *i*-PrOH/hexanes, 205, 0.5mL/min t_R = 37.8.0 min, 56.11 min

Hydrogenation of Nitroketone 1:

A mixture of nitroketone **1** (100 mg, 0.48 mmol) and 10% $Pd(OH)_2$ on carbon in 20 mL of anhydrous methanol was hydrogenated at 60 psi for 50 h by using a Parr apparatus. The solution was filtered and concentrated to give pyrrolidine **8**[5] (67 mg, 0.42 mmol, 87%) as a liquid (dr = 3 : 1).

Stereochemistry

Relative (*syn*) and absolute configuration of ketone **3** was determined by comparison with known ^{1}H-NMR data and optical rotation values ($[\alpha]_D$ = -9.7, c = 1 ($CHCl_3$)).[3] Absolute configurations of products **1**–**7** have been tentatively assigned accordingly. The stereochemistry of derivative **4** has been assigned by analogy with **3**. The relative *syn*-configuration of ketone **2** has been determined by comparison with known NMR data.[2] Assignment of *syn* relative configuration to ketone **5** is based on the known preference of 2-substituted cyclohexane nitronate ions for equatorial protonation.[6] The observed steroselectivities are consistent with models **A** and **B**.[7,6]



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