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NEW SYNTHESIS OF LACTAMS AND SPIROLACTAMS RADICAL CYCLIZATION INDUCED BY MANGANESE(III) ACETATE

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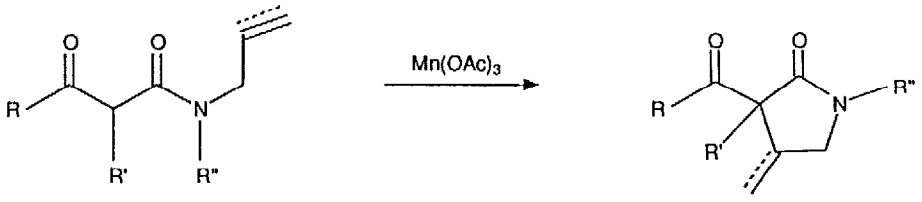
Summary : Lactams were produced by treatment of N,N-unsaturated dialkyl-β-oxoamides by $Mn(OAc)_3$.

Many synthetically derived azaspiro|5.5|undecanes and |4.5|decanes exhibit various biological properties[1]. Recently, three interesting spirocyclic alkaloids such as nitramine, isonitramine and sibirine were isolated[2]. Due to their potential biological activities, we embarked on the synthesis of azaspirocyclic skeletons.

Manganese (III) acetate [$Mn(OAc)_3$] is able to oxidize ω-unsaturated-β-dicarbonyl compounds[3] producing a radical which can cyclize in five[4-5], six[5-6], seven or eight-membered ring[7].

As intra and intermolecular free radical addition reactions can be used to construct carbon-carbon bonds in alkaloid synthesis[8], and as a large number of functional groups are tolerated in free radical conditions[9], the formation of lactams and spirolactams has been envisaged by intramolecular oxidative radical cyclization of N,N-unsaturated dialkyl-β-oxoamides.

We wish to report here a regio- and stereo-controlled formation of substituted lactams and spirolactams 2 by treatment of N,N-unsaturated dialkyl-β-oxoamides 1[10] by $Mn(OAc)_3$.



1 2

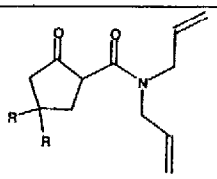
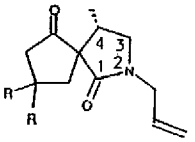
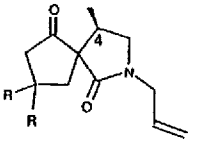
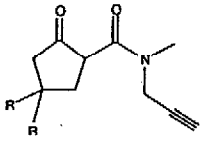
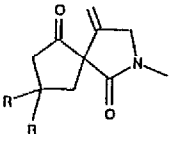
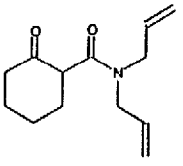
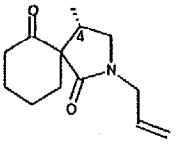
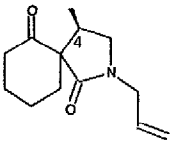
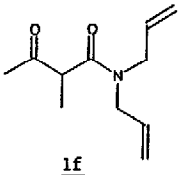
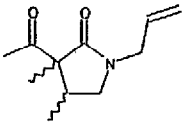
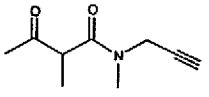
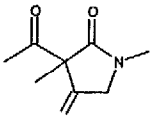
The reaction is general as shown in Table I. Monocyclic lactams 2f-2g[11] can be isolated from aliphatic β-ketoamides 1f-1g and more interestingly azaspiro |4.4| nonane and azaspiro |5.4| decane derivatives are obtained from 1a-1e. All the cyclization products can be rationalized according to Baldwin's rules[12] by a 5 exo trig or 5 exo dig process.

Treatment of 1c and 1d by $Mn(OAc)_3$ allow the formation of functionalized spirolactams 2c[13] and 2d[14].

When the oxidative radical cyclization occurs from allylamino compounds 1a, 1b, 1e, two

Table I

Mn III Mediated radical cyclization of unsaturated β-ketoamides compounds

Compound 1	Cyclized product 2	
		
1a R = H 1b R = CH_3	2a : 47% 2b : 47%	2a' : 3% 2b' : 3%
		
1c R = H 1d R = CH_3	2c : 60% 2d : 55%	
		
1e	2e : 30%	2e' : 10%
		
1f	2f : 40%	
		
1g	2g : 40%	

Experimental part:

To a degassed solution of $Mn(OAc)_3$ (1.93×10^{-3} mole, 2 eq) in ethanol (5 ml) was added dropwise a degassed solution of 1a (0.966×10^{-3} mole, 1 eq) in ethanol (5 ml). After one hour at room temperature, the solution was filtered on Celite, evaporated, extracted with ethyl acetate and purified either by flash chromatography or on TLC plates.

diastereoisomers are obtained. The separation of these isomers is easily carried out by flash chromatography. The stereochemistry is determined by ^1H NMR. For the minor isomers 2a', 2b', 2e', the ^1H NMR spectra show a doublet for the methyl group attached on C-4 at 0.96 ppm for 2a'[15] and 2b'[16], and at 0.99 ppm for 2e'[17]. These methyl groups are at higher field than the corresponding methyl groups of the stereoisomers 2a[18], 2b[19] (1.03 ppm) and 2e[20] (1.16 ppm). The higher field values for the chemical shift of the methyl group of 2a', 2b' and 2e' is due to the anisotropic effect of the carbonyl group of the cyclopentanone and of the cyclohexanone. The stereoselectivity observed for the azaspiro |4.4| nonane decreases when an azaspiro |4.5| decane is formed (Table I).

The success of the reaction strongly depends on the reaction conditions. We found that the best yields were obtained in ethanol. Solvents such as acetic acid and acetonitrile could be also used, but the cyclization products were isolated in lower yield (12% and 17% respectively). Moreover, a careful degassing of the solution and the use of anhydrous $Mn(OAc)_3$ are necessary for obtaining 2 in good yields.

The oxidative cyclization of N,N-unsaturated dialkyl oxoamides allows the formation of substituted lactams, and should be a very convenient method for the preparation of natural azaspirannic alkaloids.

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11. 2f : IR ($CHCl_3$): 1720, 1695, 1480, 1435, 1410, 1360, 1125 cm^{-1} ; ^1H NMR ($CDCl_3$) 300 MHz: 1.04 (d, 3H, J=7 Hz), 1.42 (s, 3H), 2.15 (s, 3H), 2.20-2.31 (m, 1H), 3.08-3.40 (m, 2H), 3.86-4.05 (m, 2H), 5.20-5.30 (m, 2H), 5.70-5.84 (m, 1H) ; ^{13}C NMR ($CDCl_3$) 75 MHz: 12.97, 19.45, 29.26, 39.43, 45.51, 51.40, 60.88, 118.30, 131.91, 174.47, 207.16 ; M.S. m/e = 195 (18%), 138 (100%) ; Anal. Calcd. for $C_{11}H_{17}NO_2$: C 67.66; H 8.78; N 7.17; Found: C 67.54; H 8.89; N 7.29.
    2g : IR ($CHCl_3$): 1710, 1650, 1460, 1435, 1285, 1060 cm^{-1} ; ^1H NMR ($CDCl_3$) 300 MHz: 1.44 (s, 3H), 2.15 (s, 3H), 3.00 (s, 3H), 4.05-4.21 (m, 2H), 5.06-5.25 (m, 2H) ; ^{13}C NMR ($CDCl_3$) 75 MHz: 19.42, 25.76, 29.47, 52.92, 62.00, 110.62, 142.29, 173.18, 202.20 ; M.S. m/e = 167 (0.25%), 124

(100%); Anal. Calcd. for $C_9H_{13}NO_2$: C 64.65; H 7.84; N 8.38; Found: C 64.16; H 7.80; N 8.42.
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13. 2c: IR ($CHCl_3$): 1730, 1680, 1650, 1485, 1425, 1400, 1310, 1280 cm^{-1} ; ^1H NMR ($CDCl_3$) 300 MHz: 1.95-2.70 (m, 6H), 2.90 (s, 3H), 3.83-4.21 (m, 2H), 5.01-5.12 (m, 2H) ; ^{13}C NMR ($CDCl_3$) 75 MHz: 20.13, 29.57, 32.83, 37.82, 53.49,63.24, 108.04, 143.81, 172.06, 213.96 ; M.S. m/e = 179 (39%), 124 (100%); Anal. Calcd. for $C_{10}H_{13}NO_2$: C 67.01; H 7.31; N 7.82; Found: C 66.86; H 7.48; N 7.86.
14. 2d: IR ($CHCl_3$): 1740, 1690, 1660, 1435, 1410, 1150 cm^{-1} ; ^1H NMR ($CDCl_3$) 300 MHz: 1.16 (s, 3H), 1.27 (s, 3H), 1.90 (d, 1H,J=13.5 Hz), 2.26 (d, 1H, J=16.5 Hz), 2.37 (d, 1H, J=16.5 Hz), 2.56 (d, 1H, J=13.5 Hz), 2.94 (s, 3H), 3.83-4.23 (m, 2H), 5.05-5.15 (m, 2H); ^{13}C NMR ($CDCl_3$) 75 MHz: 28.75, 29.48, 29.57, 32.98, 45.60, 52.95, 53.55, 64.95, 107.81, 144.11, 171.73, 211.78; M.S. m/e = 207 (20%), 124 (100%); Anal. Calcd. for $C_{12}H_{17}NO_2$: C 69.53; H 8.27; N 6.76; Found: C 69.61; H 8.42; N 6.88.
15. 2a': IR ($CHCl_3$): 1740, 1690, 1480, 1410, 1270, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) 300 MHz: 0.96 (d, 3H, J=7.5 Hz), 1.84-2.65 (m, 7H), 2.81-2.87 (m, 1H), 3.66-3.73 (m, 1H), 3.82-4.01 (m, 2H), 5.16-5.29 (m, 2H), 5.64-5.80 (m, 1H); ^{13}C NMR ($CDCl_3$) 75 MHz: 15.56, 19.38, 27.97, 32.91, 37.60, 45.18, 51.90, 62.66, 117.69, 131.94, 137.00, 217.05; M.S. m/e = 207 (40%), 152 (100 %); Anal. Calcd. for $C_{12}H_{17}NO_2$: C 69.53; H 8.27; N 6.76; Found: C 69,59; H 8,45; N 6.90.
16. 2b': IR ($CHCl_3$): 1720, 1670, 1500, 1480, 1430, 1260, 1040 cm^{-1} ; ^1H NMR ($CDCl_3$) 300 MHz: 0.96 (d, 3H, J=7 Hz), 1.11 (s, 3H), 1.17 (s, 3H), 1.84-2.82 (m, 5H), 3.10-3.29 (m, 2H), 3.75-3.96 (m, 2H), 5.09-5,23 (m, 2H), 5.60-5.75 (m, 1H); ^{13}C NMR ($CDCl_3$) 75 MHz: 17.55, 28.99, 29.80, 34.06, 34.45, 40.78, 52.65, 53.57, 55.22, 64.40, 117.90, 132.20, 173.25, 216.54; M.S. m/e = 235 (100%), 152 (100%); Anal. Calcd. for $C_{14}H_{21}NO_2$: C 71.40; H 8.99; N 5.95; Found: C 71.31; H 9.05; N 5.97.
17. 2e': IR ($CHCl_3$): 1700, 1675, 1495, 1455, 1420, 1255, 1125 cm^{-1} ; ^1H NMR ($CDCl_3$) 300 MHz: 0.99 (d, 3H, J=7 Hz), 1.63-2.50 (m, 7H), 2.83 (dd, 1H, J=7 and 9.5 Hz), 2.96-3.10 (m, 2H), 3.35 (dd, 1H, J=7 and 9.5 Hz), 3.83-3.93 (m, 2H), 5.13-5.21 (m, 2H), 5.63-5.87 (m, 1H); ^{13}C NMR ($CDCl_3$) 75 MHz: 13.47, 20.61, 26.76, 30.19, 31.56, 40.30, 45.31, 50.46, 61.50, 117.87, 132.06, 172.46, 208.37; M.S m/e = 221 (50%), 97 (100%); Anal. Calcd. for $C_{13}H_{19}NO_2$: C 70.55; H 8.65; N 6.33; Found: C 70.36; H 8.74; N 6.39.
18. 2a: IR ($CHCl_3$): 1740, 1690, 1480, 1430, 1410, 1270, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) 300 MHz: 1.03 (d, 3H, J=7.5 Hz), 1.84-2.65 (m, 7H), 3.20-3.35 (m, 2H), 3.82-4,01 (m, 2H), 5.16-5.29 (m, 2H), 5.64-5.80 (m, 1H); ^{13}C NMR ($CDCl_3$) 75 MHz: 12.39, 20.20, 32.32, 38.34, 39.63, 45.31, 51.14, 61.89, 117.43, 132.00, 137.10, 216.61; M.S m/e = 207 (40%), 152 (100%); Anal. Calcd. for $C_{12}H_{17}NO_2$: C 69.53; H 8.27; N 6.76; Found: C 69.58; H 8.43; N 6.93.
19. 2b: IR ($CHCl_3$): 1720, 1670, 1500, 1480, 1430, 1260, 1040 cm^{-1} ; ^1H NMR ($CDCl_3$) 300 MHz: 1.03 (d, 3H, J=7 Hz), 1.11 (s, 3H), 1.17 (s, 3H), 1.61 (d, 1H, J=13 Hz), 2.02 (d, 1H, J=17 Hz), 2.13-2.35 (m, 1H), 2.17 (d, 1H, J=17 Hz), 2.40 (d, 1H, J=13 Hz), 3.10-3.20 (m, 2H), 3.75-3.96 (m, 2H), 5.09-5.23 (m, 2H), 5.60-5.75 (m, 1H); ^{13}C NMR ($CDCl_3$) 75 MHz: 12.10, 29.20, 30.23, 33.69, 39.45, 45.78, 51.21, 51.44, 55.22, 63.62, 117.70, 132.31, 173.42, 215.49; M.S. m/e = 235 (100%), 152 (100%); Anal. Calcd. for $C_{14}H_{21}NO_2$: C 71.40; H 8.99; N 5.95; Found: C 71.21; H 9.06; N 5.95.
20. 2e: IR ($CHCl_3$): 1700, 1675, 1495, 1455, 1420, 1225, 1125, 920 cm^{-1}; ^1H NMR ($CDCl_3$) 300 MHz: 1.16 (d, 3H, J=7 Hz), 1.66-2.63 (m, 8H), 3.09-3.30 (m, 2H), 3.81-3.91 (m, 2H), 5.14-5.26 (m, 2H), 5.65-5.98 (m, 1H); ^{13}C NMR ($CDCl_3$) 75 MHz: 13.82, 20.91, 24.31, 34.23, 39.27, 41.48, 45.18, 51.28, 61.63, 117.44, 131.96, 173.58, 208.64; M.S. m/e = 221 (50%), 97 (100%); Anal. Calcd. for $C_{13}H_{19}NO_2$: C 70.55; H 8.65; N 6.33; Found: C 70.20; H 8.80; N 6.38.

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