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Microwave- and ultrasound-assisted oxidation of bio-active limonoids

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Abstract—Tetranortriterpenoids from *Azadirachta indica* A. Juss and *Soymida febrifuga* (Meliaceae), have been selectively oxidized to single major products which exhibit bioactivity higher than the parent compounds, comparable to that of azadirachtin A. The reaction proceeds to completion in less than 15 min and 1 min on being assisted by ultrasound and microwave irradiation, respectively. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

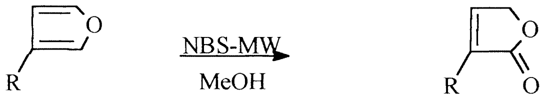
The neem triterpenoids are one of the most interesting groups of anti-insect phytochemicals which are promising as new, natural pesticides. Neem oil from leaves and seeds normally contains major triterpenoids like salannin, nimbin, desacetyl nimbin, desacetyl salannin and nimonol apart from the highly active antifeedant azadirachtin.[1,2] Connolly et al. isolated oxidized products of salannin and nimbin from neem seeds,[3] where the furan ring had been converted to an α,β-unsaturated lactone. These oxidized products showed better antifeedant activity compared with the parent compounds.[4] Oxidation of the furan ring into a butyrolactone in a similar type of limonoid, gedunin, was effected using the oxidant, *N*-bromosuccinimide[5] and resulted in a poor yield and took a long time for completion.[6]

In recent years, the use of microwave and ultrasound irradiation in organic reactions has increased due to shorter reaction times, higher yields and operational simplicity.[7–9] In the present study, the possibility of applying microwave and ultrasound irradiation to carry out selective oxidation of the furan ring in triterpenoids has been explored.

2. Results and discussion

Tetranortriterpenoids such as salannin **1**, nimbin **2**, desacetyl nimbin **3**, nimonol **4** and methyl angolansate **5** were subjected to oxidation using *N*-bromosuccinimide (Scheme 1) under (a) stirring at 0°C, (b) ultrasound, and (c) microwave irradiation. In all these cases, the furan moiety present in these limonoids underwent a partial oxidation leading to a butyrolactone in 48 h, 15 min and less than a minute, respectively (Table 1). The structures of the products were authenticated by ^{1}H, ^{13}C and 2D NMR studies[15–19]. Furthermore, for one of the products (salannolactone) the structure was confirmed by X-ray crystallography (Fig. 1).[10,11]

A perusal of the ^{13}C NMR of the products revealed the presence of an additional lactone carbonyl resonating at δ 170–173 ppm in addition to the carbonyl group/s present in the starting materials. DEPT-135 confirmed an additional methylene carbon at δ 70.2 ppm, corresponding to an oxymethylene group whose CH$_2$ was observed as a doublet at 4.7 ppm (^{1}H–^{13}C COSY). These protons showed a connectivity with a proton at δ 7.28 ppm (^{1}H–^{1}H COSY) whose carbon resonated at δ 144.8 ppm thereby confirming it to be an olefinic methine. The additional quaternary carbon resonating



Scheme 1.

Keywords: tetranortriterpenoids; *N*-bromosuccinimide; antifeedancy; ultrasound; microwave; α,β-unsaturated lactone.

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Table 1. Oxidation of limonoids

S. No.	Compound	Conventional oxidation		Ultrasound		Microwave	
		Time (h)	Yield (%)	Time (min)	Yield (%)	Time (s)	Yield (%)
1	Salannin	48	36	15	60	30	72
2	Nimbin	32	40	15	62	15	76
3	Desacetyl nimbin	30	42	12	56	15	66
4	Nimonol	40	36	12	62	60	76
5	Methyl angolansate	41	40	15	58	60	62

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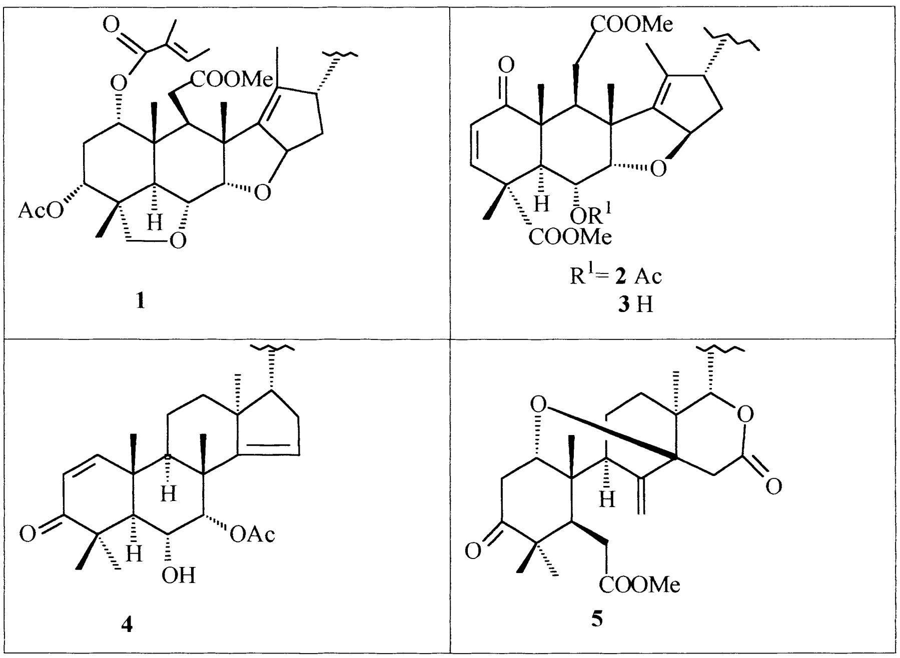

at δ 132.5 ppm was assigned as the other olefinic methine. The above results confirmed the presence of the butyrolactone rings.

The products exhibited higher antifeedant activity than the parent compounds when tested against *Spodoptera litura* with activities that were comparable to that of azadirachtin A, the most powerful natural antifeedant isolated from *Azadirachta indica* A. Juss.[12]

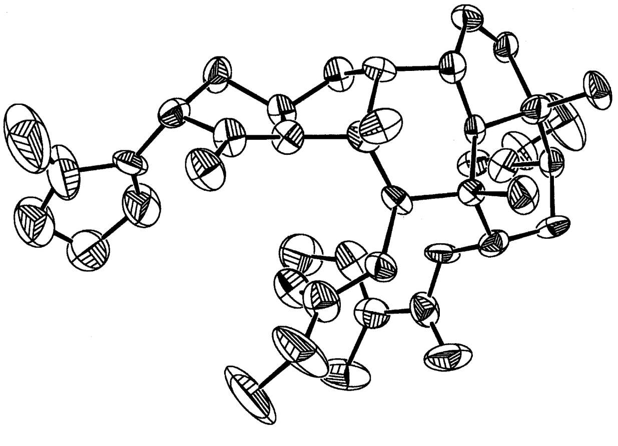

Figure 1. ORTEP diagram of salannolactone **1** drawn at 30% probability.

3. General experimental procedure

To a solution of the tetranortriterpenoid (0.1 mmol) in MeOH (2 ml), freshly crystallized *N*-bromosuccinimide (0.1 mmol) was added and the reaction mixture was placed either in an ice bath with a magnetic stirrer for 48 h, or an ultrasonicator (38 kHz) at 300 K for 15 minutes or under microwave irradiation (2450 MHz) for a minute. The reaction was monitored by TLC. The solvent was removed under reduced pressure. The crude product was chromatographed on a silica gel column using 1:1 ethyl acetate: hexane as eluant to obtain the pure products.

3.1. Isolation of tetranortriterpenoids

Salannin, nimbin, and desacetyl nimbin were isolated from neem seed extract by preparative HPLC.[12] Nimonol was isolated from uncrushed neem leaves following the procedure established earlier in our laboratory.[13] Methyl angolansate was isolated from the seeds of *Soymida febrifuga* as reported in the literature.[14]

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11. Details of the crystal structure of salannolactone **1**: Crystal system: orthorhombic; space group: $P2_12_12_1$; unit cell dimensions: $a=7.531(2)$, $b=20.308(6)$, $c=21.193(8)$ Å; final R indices $[I>2\sigma(I)]$: $R_1=0.0869$, $wR_2=0.1819$. Data deposited with the Cambridge Crystallographic Data Centre.
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15. Salannolactone **1**
Mp 156°C; UV ($CHCl_3$) $\lambda_{\max}$: 240 nm (ε 9638), 245 nm (ε 8852), 254 nm (ε 7405); IR ($CHCl_3$) $\nu_{\max}\backslash\mathrm{cm}^{-1}$ 3376, 2976, 2880, 1760, 1708, 1696, 1651, 1596, 1488, 1465, 1379, 1315, 1273, 1068, 1001, 969, 880, 838, 646, 611; ^{1}H NMR ($CDCl_3$) (δ, ppm) 7.28 (d, 1H, $J=5.6$ Hz), 6.95 (m, 1H), 5.33 (t, 1H, $J=6.1$ Hz), 4.96 (d, 1H, $J=2.6$ Hz), 4.76 (d, 1H, $J=5.3$ Hz), 4.71 (d, 2H, $J=5.0$ Hz), 4.21 (d, 1H, $J=3.2$ Hz), 3.96 (dd, 1H, $J=12.7$, 3.2 Hz), 3.71 (m, 1H), 3.66 (d, 1H, $J=7.3$ Hz), 3.58 (m, 1H), 3.52 (s, 3H), 2.77 (d, 1H, $J=13$ Hz), 2.68 (m, 1H), 2.35 (m, 2H), 2.21–2.31 (m, 4H), 1.93 (s, 3H), 1.87 (s, 3H), 1.81 (s, 3H), 1.73 (s, 3H), 1.28 (s, 3H), 1.23 (s, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$) (δ, ppm) 174.2, 173.3, 170.3, 166.7, 149.0, 144.8, 137.3, 135.4, 132.4, 129.0, 87.4, 85.7, 77.6, 72.4, 71.5, 71.3, 70.2, 51.6, 49.3, 48.8, 42.7, 40.6, 40.0, 39.9, 30.7, 29.7, 27.4, 20.8, 19.6, 16.9, 15.0, 14.4, 13.1, 11.9; m/z: 612 (M$^+$).
16. Nimbinlactone **2**
Mp 145–148°C; UV ($CHCl_3$) $\lambda_{\max}$: 240 nm (ε 9448), 254 nm (ε 8109); IR ($CHCl_3$) $\nu_{\max}\backslash\mathrm{cm}^{-1}$ 3343, 2960, 2853, 1751, 1720, 1654, 1570, 1435, 1309, 1089, 976, 889, 886, 645, 607; ^{1}H NMR ($CDCl_3$) (δ, ppm) 7.23 (d, 1H, $J=5.1$ Hz), 6.35 (d, 1H, $J=10.1$ Hz), 5.87 (d, 1H $J=10.1$ Hz), 5.40 (t, 1H), 5.21 (dd, 1H, $J=2.9$, 12.3 Hz), 4.78 (d, 2H, $J=5.1$ Hz), 4.08 (d, 1H, $J=3.1$ Hz), 3.73 (s, 3H), 3.71 (s, 3H), 3.68 (m, 1H), 3.57 (t, 1H, $J=6$ Hz), 2.88 (m, 1H), 2.72 (m, 1H), 2.22 (dd, 1H, $J=12.7$, 3.9 Hz), 2.13 (m, 1H), 2.04 (s, 3H), 1.99 (m, 1H), 1.73 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 1.29 (s, 3H); ^{13}CNMR ($CDCl_3$) (δ, ppm) 201.8, 174.5, 174.4, 174.4, 170.5, 148.6, 147.8, 145.1, 134.9, 132.9, 125.8, 86.5, 84.6, 70.3, 68.4, 53.1, 51.7, 48.6, 48.1, 48.0, 47.1, 41.4, 40.1, 38.8, 34.3, 20.9, 17.1, 16.7, 16.5, 13.1; m/z: 556 (M$^+$).
17. Desacetylnimbinolactone **3**
Mp 130–132°C; UV ($CHCl_3$) $\lambda_{\max}$: 245 nm (ε 6618), 254 nm (ε 4314); IR ($CHCl_3$) $\nu_{\max}\backslash\mathrm{cm}^{-1}$ 3343, 2975, 2848, 1748, 1709, 1645, 1575, 1445, 1310, 1024, 970, 880, 842, 647, 611; ^{1}H NMR ($CDCl_3$) (δ, ppm) 7.23 (d, 1H, $J=5.1$ Hz), 6.35 (d, 1H, $J=10$ Hz), 5.78 (d, 1H, $J=10$ Hz), 5.31 (t, 1H), 4.71 (d, 2H, $J=5.1$ Hz), 4.08 (d, 1H, $J=3.1$ Hz), 3.83 (dd, 1H, $J=12.3$, 2.9 Hz), 3.63 (s, 3H), 3.60 (s, 3H), 3.54 (m, 1H), 3.26 (t, 1H, $J=6$ Hz), 2.74 (m, 1H), 2.56 (m, 1H), 2.22 (dd, 1H, $J=12.1$, 3.9 Hz), 2.17 (brs, 1H, D_2O exchangeable), 2.13 (m, 1H), 1.99 (m, 1H), 1.67 (s, 3H), 1.52 (s, 3H), 1.20 (s, 3H), 1.19 (s, 3H,); ^{13}CNMR ($CDCl_3$) (δ, ppm) 202.4, 175.4, 174.3, 174.3, 149.2, 148.2, 145.2, 134.8, 132.6, 126.2, 87.5, 86.3, 70.4, 65.9, 53.0, 51.7, 48.7, 47.9, 47.9, 47.4, 43.4, 39.9, 39.2, 34.3, 17.4, 17.1, 16.2, 13.0; m/z 514 (M$^+$).
18. Nimonolactone **4**
Mp 130–132°C; UV ($CHCl_3$) $\lambda_{\max}$: 217 nm (ε 7220); IR ($CHCl_3$) $\nu_{\max}\backslash\mathrm{cm}^{-1}$ 3352, 2860, 2848, 1742, 1712, 1698, 1583, 1445, 1310, 1024, 970, 880, 842, 647, 611; ^{1}H NMR ($CDCl_3$) (δ, ppm) 7.26 (d, 1H, $J=4.8$ Hz), 7.11 (d, 1H, $J=10$ Hz), 5.88 (d, 1H, $J=10$ Hz), 5.54 (d, 1H, $J=2.8$ Hz), 5.46 (dd, 1H, $J=12.3$, 2.3 Hz), 4.89 (d, 2H, $J=4.8$ Hz), 4.06 (dd, 1H, $J=11.5$, 3 Hz), 2.87 (1H, d, $J=7.1$ Hz), 2.71 (m, 1H), 2.66 (m, 1H), 2.38 (m, 1H), 2.31 (m, 1H), 2.18 (s, 3H), 2.03 (m, 1H), 1.89 (m, 1H), 1.78 (m, 1H), 1.65 (m, 1H), 1.78 (bs, 1H, D_2O exchangeable), 1.32 (s, 3H), 1.29 (s, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$) (δ, ppm) 204.8, 174.1, 170.3, 159.8, 157.2, 146.6, 133.8, 126.0, 119.8, 73.7, 71.6, 70.3, 50.8, 47.3, 46.4, 44.9, 44.9, 41.0, 34.0, 33.5, 32.4, 31.8, 26.8, 21.7, 20.9, 20.6, 20.6, 16.2; m/z 468 (M$^+$).
19. Methyl angolansatelactone **5**
Mp 114–116°C; UV ($CHCl_3$) $\lambda_{\max}$: 298 nm (ε 3782), 227 nm (ε 4395); IR ($CHCl_3$) $\nu_{\max}\backslash\mathrm{cm}^{-1}$ 2860, 2214, 1768, 1718, 1687, 1649, 1560, 1468, 1445, 1389, 1335, 1283, 1068, 1051, 961, 887, 646, 611; ^{1}H NMR ($CDCl_3$)(δ, ppm) 7.55 (d, 1H, $J=5.1$ Hz), 5.63 (s, 1H), 5.15 (s, 2H), 4.88 (d, 2H, $J=5.1$ Hz), 3.70 (s, 3H), 3.46 (dd, 1H, $J=11.6$, 3.8 Hz), 2.94 (m, 1H), 2.89 (m, 1H), 2.85 (m, 1H), 2.63 (m, 1H), 2.56 (m, 1H), 2.25 (m, 2H), 2.18 (m, 1H), 2.16 (m, 1H), 1.28 (m, 1H), 1.21 (m, 1H), 1.17 (s, 3H), 1.14 (m, 1H), 1.08 (s, 3H), 0.90 (s, 3H), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$) (δ, ppm) 212.7, 173.5, 171.4, 169.5, 150.7, 145.3, 130.5, 111.7, 79.5, 78.1, 77.6, 70.4, 51.9, 49.3, 47.8, 43.9, 42.8, 39.5, 39.5, 33.6, 32.8, 28.8, 26.5, 23.3, 21.4, 21.2, 13.5; m/z: 486 (M$^+$).