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REDUCTION OF ALIPHATIC NITRAMINES. APPROACH TO THE SYNTHESIS OF NITROSAMINES AND AMINES

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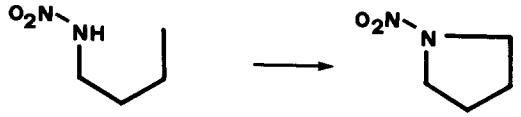
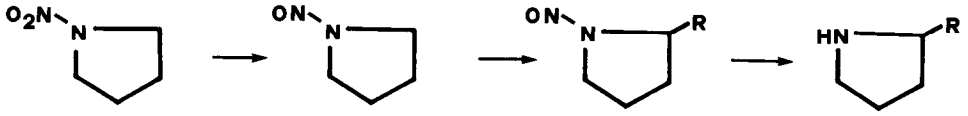
Summary: Deoxygenation of several aliphatic nitramines with tributyltin hydride in the presence of AIBN led to the formation of the corresponding nitrosamines. The nitrosamines underwent denitrosation when submitted to further treatment with tributyltin hydride. The 19-methyl steroid (9) was synthesized by α-alkylation of the nitrosamine (2).

Interest in nitrosamines has increased recently since their role as environmental carcinogens became apparent,[1] and because of their interesting utility in organic synthesis particularly for the umpolung of amine reactivity.[2] We have recently reported the synthesis of 1,4-nitroepimine compounds by photolysis of N-iodonitramines generated "in situ" by reaction of the corresponding primary nitramines with lead tetraacetate and iodine,[3] or iodosobenzene diacetate and iodine (eq. 1).[4]

It is known that nitramines are not suitable derivatives to produce umpolung of amine reactivity,[5] whereas nitrosamines are. To achieve the sequence shown in eqs. 1 and 2, formation of α-alkyl pyrrolidines from primary amines, we were prompted to find a reducing agent capable of transforming aliphatic nitramines into the corresponding nitrosamines, as we were unable to find a description of this reaction.

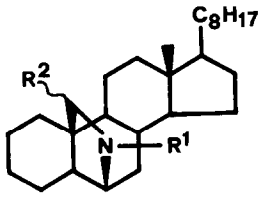


(1)

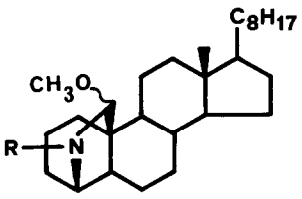


(2)

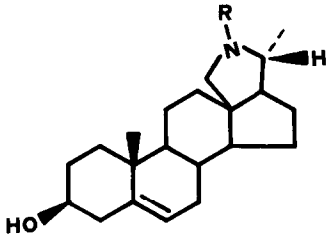
The reduction of several aliphatic nitramines with the system n-Bu_3SnH/azobisisobutyronitrile (AIBN) to the nitrosamines is summarized in Table I. The nitramine (1), previously obtained by intramolecular cyclization of 6β-nitramino-5α-cholestan,[4] reacts with n-Bu_3SnH/AIBN, to give the nitrosamine (2),[6] in 56% yield (entry 1). The presence of the radical initiator AIBN proved to be critical because when it was excluded the reaction did not



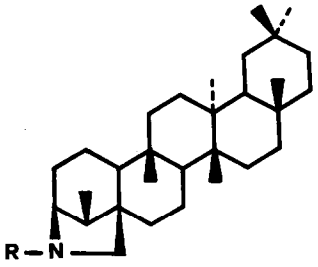
(1) $R^1 = NO_2$; $R^2 = H$
(2) $R^1 = NO$; $R^2 = H$
(9) $R^1 = NO$; $R^2 = CH_3$
(10) $R^1 = COCH_3$; $R^2 = H$



(3) $R = NO_2$
(4) $R = NO$



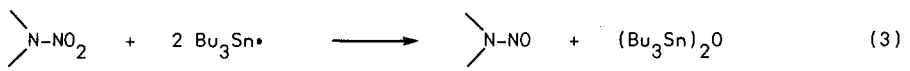
(5) $R = NO_2$
(6) $R = NO$



(7) $R = NO_2$
(8) $R = NO$
(11) $R = COCH_3$

proceed (entry 2). Attempts to improve the reaction by increasing the temperature were unsuccessful (entries 3 and 4). The reaction was extended to different steroid and triterpene derivatives as shown in entries 5-7. A typical experiment is described as follows. To a refluxing solution of n-Bu_3SnH (5 mmol) in benzene (60 ml) was added dropwise and under argon, a solution of N-nitramine (1) (1 mmol) and AIBN (1 mmol) in benzene (40 ml). The reaction was kept under reflux for 20 h while stirring, worked up as usual, and the crude product purified by chromatography on silica gel.

These results suggest that the reduction may involve the one electron transfer reaction from tin radical to the nitramine compound at the key step with deoxygenation and formation of bis(tributyltin) oxide (eq. 3) that reacts further with an excess of the hydride to afford hexabutylditin (eq. 4). As a matter of fact, the only tin compound isolated from the reaction mixture was hexabutylditin. The reaction of organotin hydrides with organotin oxides to give hexaalkyldistannanes is well documented,[11] and proceeds under similar conditions.



(3)

(4)

However, the formation of hexabutylditin directly by reaction of the hydride with the intermediate formed by addition of n-$Bu_3Sn\bullet$ to the nitramine cannot be ruled out.

TABLE I. Reduction of nitramines with n-Bu_3SnH/AIBN

Entry	Substrate	Solvent	Temp. °C;Time, h	Product (yield %)
1	**1**[4]	PhH	80;24	**2** (56)[6]
2	**1**	PhH	80;6	---[a]
3	**1**	PhH	120;6	**2** (38)
4	**1**	PhMe	110;0.5	**2** (47)
5	**3**[7]	PhH	80;2	**4** (60)[8]; **3**(20)
6	**5**[3]	PhH	80;2	**6** (59)[9]; **5**(16)
7	**7**[4]	PhH	80;1	**8** (78)[10]

[a] AIBN was omitted

The nitroso group replacement by hydrogen took place when nitrosamines **1** and **7** were submitted to the action of n-Bu_3SnH and AIBN. As displayed in Table II, these results compare favourably with those obtained when we used the methods recently described in the literature (entries 1-3)[12,13]. The corresponding amines were identified as their acetyl derivatives **10** and **11**.

Table II. Reduction of nitrosamines

Entry	Substrate	Conditions	Product (yield %)
1	**1**[4]	Bu_3SnH/AIBN; 80 °C; 6h[a]	**10** (88)
2	**1**	Zn/AcOH; 110 °C; 1.5h[12]	**10** (53)
3	**1**	$LiAlH_4$/THF; 4h then H_2/Raney-Ni; 14h[13]	**10** (40)
4	**7**[4]	Bu_3SnH/AIBN; 80 °C; 2h[a]	**11** (98)

[a] The experimental procedure was identical with that described for the reaction of the nitramines

The 19-alkyl steroids display interesting biological properties as aromatase activity inhibitors for the conversion of androgens to estrogens.[14] As proposed on eq. 2 , we accomplished the alkylation of the nitrosamine (**2**) with n-BuLi/TMEDA and ICH_3 to afford compound (**9**) (50%).[15]

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6. Compound (**2**): m.p. 100-102 °C (MeOH); $[\alpha]_D$ -33 ($CHCl_3$); IR ν_{max} ($CHCl_3$) 1330 cm^{-1}; UV λ_{max} (EtOH) 236 nm (7728); ^{1}HNMR (200 MHz, $CDCl_3$) δ 0.58 (3H, s, 13-Me), 0.83 (6H, d, J 6 Hz, 25-Me_2), 3.35 and 3.45 (2H, AB, J 14.9 Hz, 19-H_2), 4.57 (1H, d, J 4.6 Hz, 6-H); ^{13}CNMR (50.3 MHz, $CDCl_3$) δ 47.40 (19-C), 65.68 (6-C); MS m/z 414.3605 (M^+, 9%), 384.3636 (M^+-NO, 100%).
7. Compound (**3**): m.p. 170-172 °C (MeOH); $[\alpha]_D$ -46.6° ($CHCl_3$); IR ν_{max} ($CHCl_3$) 1510 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.66 (3H, s, 13-Me), 0.82 (6H, d, J 6.7 Hz, 25-Me_2), 3.68 (3H, s, 19-OMe), 4.17 (1H, d, J 3.9 Hz, 4-H), 5.05 (1H, s, 19-H); MS m/z 414 (M^+-NO_2, 9%).
8. Compound (**4**): m.p. 160-162 °C (MeOH); $[\alpha]_D$ -66° ($CHCl_3$); IR ν_{max} ($CHCl_3$) 1260 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.68 (3H, s, 13-Me), 0.83 (6H, d, J 6.6 Hz, 25-Me_2), 0.87 (3H, d, J 6.5 Hz, 20-Me), 3.64 (3H, s, 19-OMe), 4.36 (1H, d, J 3.7 Hz, 4-H), 5.14 (1H, s, 19-H); MS m/z 444.3722 (M^+, 9%).
9. Compound (**6**): m.p. 97-99 °C (n-hexane/acetone); $[\alpha]_D$ -10.5°($CHCl_3$): IR ν_{max} ($CHCl_3$) 3600, 1310 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.91 (3H, s, 10-Me), 1.49 (3H, d, J 7 Hz, 20-Me), 3.38 and 3.53 (2H, AB, J 15.9 Hz, 18-H_2), 4.54 (1H, m, $W_{1/2}$ 20 Hz, 20-H), 5.28 (1H, m, $W_{1/2}$ 14 Hz, 6-H); ^{13}CNMR ($CDCl_3$) δ 49.35 (18-C), 65.34 (20-C); MS m/z 344.2506 (M^+, 9%).
10. Compound (**8**): m.p. 300 °C ($CHCl_3$/MeOH); $[\alpha]_D$ -15°($CHCL_3$); IRν_{max} ($CHCl_3$) 1330, 3110 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ inter alia 3.10 and 3.99 (2H, AB, J 15.1 Hz, 24-H_2), 4.49 (1H, d, J 4.2 Hz, 3-H); ^{13}CNMR ($CDCl_3$) δ 51.47 (24-C), 65.95 (3-C); MS m/z 454.3883 (M^+, 5%).
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15. Compound (**9**): m.p. 177-179 °C (n-hexane); $[\alpha]_D$ 78°($CHCl_3$); IR ν_{max} ($CHCl_3$) 1250 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.58 (3H, s, 13-Me), 0.81 (6H, d, J 6.5 Hz, 25-Me_2), 0.82 (3H, d, J 6.5 Hz, 20-Me), 1.72 (3H, d, J 7.2 Hz, 19-Me), 4.22 (1H, q, J 7.5 Hz, 19-H), 4.54 (1H, d, J 4 Hz, 6-H); ^{13}CNMR ($CDCl_3$) δ 18.60 (19-Me), 60.16, 61.24 (6-C and 19-C); MS m/z 428.3772 (M^+, 80%).

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