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SYNTHESIS OF 1,4-EPIMINE COMPOUNDS. IODOSOBENZENE DIACETATE, AN EFFICIENT REAGENT FOR NEUTRAL NITROGEN RADICAL GENERATION

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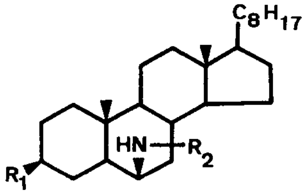
SUMMARY: Photolysis of several nitroamines, cianamines, and phosphoroamidates in the presence of iodosobenzene diacetate (IBDA) and iodine leads to neutral aminyl radicals which undergo intramolecular hydrogen abstraction to produce epimine compounds with yields that are favorably compared with those obtained with the system lead tetraacetate and iodine.

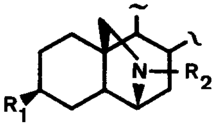
Functional groups may be introduced into suitably placed non-activated skeletal positions in organic compounds by generating reactive free radical species in close proximity to the centre to be attacked. Although the reactions initiated by alkoxy-radicals have been the subject of numerous studies,[1] comparatively little attention has been devoted to those associated with nitrogen radicals.[2] The sole reaction of this type which has proved of significant value for the preparation of cyclic amines is the Hofmann-Loeffler-Freytag reaction, based on ammonium radical intermediates.However, limited use of this reaction has been made in complex or sensitive molecules owing to the highly acidic conditions required.[3]

Recently, we reported the intramolecular functionalization of non-activated carbon atoms but through neutral aminyl radical intermediates produced by photolysis of N-iodonitroamines[4] or N-iodophosphoroamidates[5] generated "in situ" by reaction of the corresponding amine derivatives with lead tetraacetate (LTA) and iodine. We have also found that the system iodosobenzene diacetate[6] (IBDA)-iodine is an excellent reagent for alkoxy radical generation.[7]

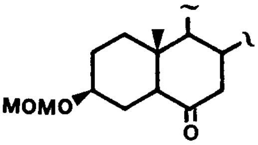
Continuing our interest in the synthesis of 1,4-epimine compounds we describe here the reaction of IBDA-iodine with N-nitroamines, N-cianamines, and N-phosphoroamidates. The results summarized in the Table compare those obtained with this reagent (A) with those from LTA-iodine system (B). Examination of the data indicates that better yields are generally observed for IBDA-iodine with exceptions for 6-phosphoramidates (3) and (4), where no reactions were observed. The cianamine group has not been used previously for the intramolecular abstraction of hydrogen and although the cyclization of cianamine (2) with IBDA-iodine leads to the epimine derivative (6, 64%) and ketone (9, 31%), attempts to cyclize the 20-cianamine (12)[8]



	R_1	R_2
1	H	NO_2
2	OMOM	CN
3	OAc	$P(O)(OEt)_2$
4	OAc	$P(O)(OBz)_2$



	R_1	R_2
5	H	NO_2
6	OMOM	CN
7	OAc	$P(O)(OEt)_2$
8	OAc	$P(O)(OBz)_2$



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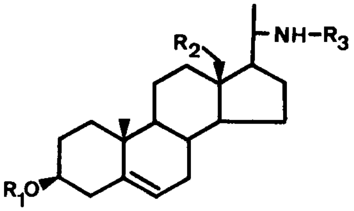
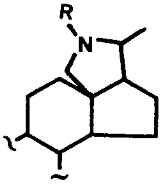
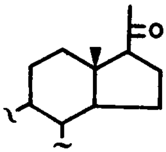


	R_1	R_2	R_3
10	Ac	H	NO_2 (20R)
11	Ac	I	NO_2 (20R)
12	OMOM	H	CN (20S)
13	Ac	H	$P(O)(OEt)_2$ (20S)
14	Ac	I	$P(O)(OEt)_2$ (20S)



R



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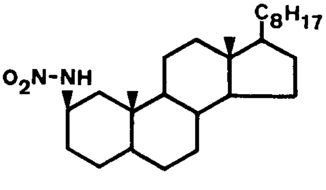
	R
15	NO_2 (20R)
16	$P(O)(OEt)_2$ (20S)



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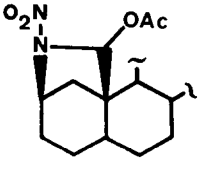

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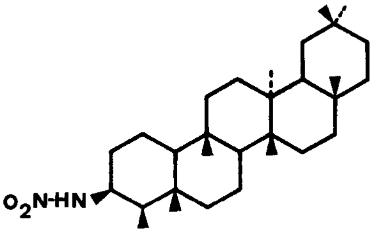

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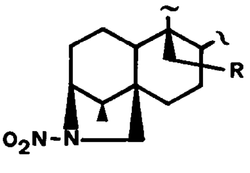

21 R=H

22 R=I

failed and only ketone (17) was obtained, and under these conditions no product derived from a hydrogen abstraction reaction was detected. Cyclization of iodoamines (11) and (14) were performed with silver acetate in acetone to give epimine compounds (15)[4] and (16),[5] respectively. Compound (22) is produced by oxidation at two different carbon atoms of nitramine (20), as previously observed[9] in the intramolecular hydrogen abstraction of alkoxy radicals. It should be noted that approximately stoichiometrical amounts of IBDA are needed to complete the reaction, especially when it is compared with the excess of the LTA required.

TABLE. Reaction of amine derivatives with iodosobenezene diacetate-iodine

Substrate	Reagent	Time (min.)	Temp. C	Product (yield %)
1[10]	**A**(1.1/0.5)	70	90	**5** (77)[12]
1	**B**(3.0/1.0)	105	90	**5** (51)
2[11]	**A**(1.5/1.0)	180	50	**6** (64)[13]; **9** (31)
2	**B**(3.0/1.0)	180	90	**6** (22) ; **9** (24)
3[5]	**A**(10.0/5.0)	120	90	No reaction
3	**B**(10.0/5.0)	120	90	**7** (100)[5]
4[5]	**A**(10.0/5.0)	120	90	No reaction
4	**B**(10.0/5.0)	120	90	**8** (100)[5]
10[4]	**A**(1.5/0.5)	70	90	**11** (47)[4]
10	**B**(3.0/1.0)	80	90	**11** (15)
13[5]	**A**(1.1/1.0)	80	50	**14** (62)[5]
13	**B**(3.0/1.0)	60	50	**14** (60) ; **16** (10)[5]
18[14]	**A**(2.0/1.0)	100	80	**19** (64)[15]
18	**B**(3.0/1.5)	180	80	**19** (50)
20[16]	**A**(2.1/1.0)	180	55	**21** (22)[17]; **22** (21)[18]
20	**B**(3.1/1.0)	90	55	**21** (21) ; **22** (20)

A: Moles of IBDA / moles of iodine per mole of substrate.

B: Moles of LTA / moles of iodine per mole of substrate.

A typical experiment is described as follows: a solution of N-nitroamine (1)(1 mmol) in cyclohexane (43 ml) containing IBDA (1.1 mmol) and iodine (0.5 mmol) was irradiated with two 100-W tungsten-filament lamps for 70 min. at 90° C. The reaction mixture was then poured into water and extracted with methylene chloride. The organic layer was washed with aqueous sodium thiosulphate and water. Silica gel column chromatography of the residue (eluant n-hexane:ethyl acetate 99:1) gave the 1,4-epimine derivative (5) in 77% yield.

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REFERENCES AND FOOTNOTES

1. K. Heusler and J. Kalvoda, **"Organic Reactions in Steroid Chemistry"**, J. Fried and J.A. Edwards, eds., van Nostrand Reinhold, New York, vol.2, p. 237 (1971); J. Kalvoda and K. Heusler, **Synthesis**, 501 (1971).
2. R.S. Neale, **Synthesis**, 1 (1971); A. Schonberg, **"Preparative Organic Photochemistry"**, Springer-Verlag. West Berlin, p. 242 (1968); M.E. Wolff, **Chem. Rev. 63**,55 (1963).
3. R.S. Neale, M.R. Walsh, and M.L. Marcus, **J. Org. Chem., 30**, 3683(1965).
4. R. Hernández, A. Rivera, J.A. Salazar, and E. Suárez, **J.C.S. Chem. Commun.**, 958 (1980).
5. C. Betancor, J.I. Concepción, R. Hernández, J.A. Salazar, and E. Suárez, **J. Org. Chem., 48**, 4430 (1983).
6. D.F. Banks, **Chem. Rev., 66**, 243 (1966); A. Varvoglis, **Chem. Soc. Rev., 10**, 377 (1981). Commercial IBDA (Aldrich, 98%) was used without purification. With this reagent the work-up is simpler and faster than with LTA, especially in large scale reactions, which often produce tars which are difficult to purify.
7. J.I. Concepción, C.G. Francisco, R. Hernández, J.A. Salazar, and E. Suárez, **Tetrahedron Letters, 25**, 1953 (1984).
8. Compound (12):m.p. 167-9°C (MeOH); $[\alpha]_D$ -40°(CHCl$_3$); IR ν_{max} (CHCl$_3$) 3390, 2215 cm^{-1}; ^{1}HNMR (CDCl$_3$)δ 4.36 (1H, m, $W_{1/2}$ 20 Hz, 20β-H);MS m/z 324 (M$^+$-MOMOH, 100%).
9. E. Wenkert and B.L. Mylari, **J. Am. Chem. Soc., 89**, 174 (1968).
10. Compound (1): amorphous; $[\alpha]_D$ +14°(CHCl$_3$); IR ν_{max} (CHCl$_3$) 3410, 1570, 1350 cm^{-1}; ^{1}HNMR (CDCl$_3$)δ <u>inter alia</u> 4.25 (1H, m, $W_{1/2}$9 Hz, 6α-H), 0.95 (3H, s, 10-Me); MS m/z 386 (M$^+$-NO$_2$, 30%).
11. Compound (2): m.p. 130°C (MeOH);$[\alpha]_D$ -25°(CHCl$_3$); IR ν_{max} (CHCl$_3$) 3390, 2200 cm^{-1}; ^{1}NMR (CDCl$_3$)δ 3.35 (4H, 6α-H, MeO); ^{13}CNMR (CDCl$_3$)δ <u>inter alia</u> 115.78 (CN), 57.53 (6-C); MS m/z 472.3958 (M$^+$, 12%).
12. Compound (5): m.p. 117-8°C (MeOH);$[\alpha]_D$ +56°(CDCl$_3$); IR ν_{max} (KBr) 1570, 1350 cm^{-1}; ^{1}HNMR (CDCl$_3$)δ 4.36 (1H, m, $W_{1/2}$9 Hz, 6α-H), 3.79, 3.65 (AB, J 13 Hz, 19-H$_2$); ^{13}CNMR (CDCl$_3$) δ 65.49 (6-C), 51.45 (19-C); MS m/z 384.3795 (M$^+$-NO$_2$, 100%).
13. Compound (6): amorphous; IR ν_{max} (CHCl$_3$) 2200 cm^{-1}; ^{1}HNMR (CDCl$_3$)δ 3.54 (1H, d, J 4.3 Hz, 6α-H), 3.33, 3.14 (AB, J 9.5 Hz, 19-H$_2$); ^{13}CNMR (CDCl$_3$)δ 117.44 (CN), 66.14 (6-C), 51.76 (19-C); MS m/z 470.3826 (M$^+$, 19%).
14. Compound (18): m.p. 153-5°C (MeOH); $[\alpha]_D$ -23° (CHCl$_3$); IR ν_{max} (CHCl$_3$) 3410, 1570, 1350 cm^{-1}; ^{1}HNMR (CDCl$_3$) δ4.23 (1H, m, $W_{1/2}$ 18 Hz, 2α-H), 0.83 (3H, s, 10-Me); MS m/z 432 (M$^+$, 2%).
15. Compound (19): m.p. 140-2°C (MeOH); $[\alpha]_D$ +44° (CHCl$_3$); IR ν_{max} (CHCl$_3$) 1750, 1515, 1360 cm^{-1}; ^{1}HNMR (CDCl$_3$) δ6.63 (1H, s, 19-H), 4.27 (1H, m, $W_{1/2}$ 20 Hz, 2α-H), 2.13 (3H, s, OAc); MS m/z 441 (M$^+$-NO$_2$H, 3%).
16. Compound (20): m.p. 205-7°(Acetone); $[\alpha]_D$ +45°(CHCl$_3$); IR ν_{max} (CHCl$_3$) 3410, 1570 cm^{-1}; ^{1}HNMR (CDCl$_3$) δ4.22(1H, m, $W_{1/2}$ 15 Hz, 3α-H); MS m/z 472 (M$^+$, 3%).
17. Compound (21): m.p. >300°C (CHCl$_3$/MeOH);$[\alpha]_D$ +56°(CHCl$_3$); IR ν_{max} (CHCl$_3$) 1480 cm^{-1}; ^{1}HNMR (CDCl$_3$)δ 4.25,3.42 (AB, J 12.4 Hz, 24-H$_2$), 4.21 (1H, d, J 3.9 Hz, 3α-H); ^{13}CNMR (CDCL$_3$)δ 55.74 (24-C); MS m/z 470.3910 (M$^+$, 2%).
18. Compound (22): m.p. 176-8°C (CHCl$_3$/MeOH); $[\alpha]_D$ -10° (CHCl$_3$); IR ν_{max} (CHCl$_3$) 1485 cm^{-1}; ^{1}HNMR (CDCl$_3$) δ 4.30, 3.58 (AB, J 12.4 Hz, 24-H$_2$), 4.23 (1H, d, J 3.7 Hz, 3α-H), 3.87, 3.47 (AB, J 11.6, 25-H$_2$); ^{13}CNMR (CDCl$_3$) δ 56.41 (24-C), 11.59 (25-C); MS m/z 468.3705 (M$^+$-HI, 1%).

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