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SYNTHESIS OF NEW 5-NITROTETRAHYDRO-1,3-OXAZINE DERIVATIVES VIA ELECTRON-TRANSFER REACTIONS †

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Abstract - 5-Nitrotetrahydro-1,3-oxazine salts are found to be useful nucleophiles for $S_{RN}1$ reactions with p-nitrobenzyl chloride, 2,2-dinitropropane and 1-methyl-2-chloromethyl-5-nitroimidazole. From C-alkylation products, base-promoted nitrous acid elimination and electron-transfer elimination of the two nitro groups afford new tetrahydro-1,3-oxazines with respectively a tri- and tetrasubstituted double bond at the 5 position. These new tetrahydro-1,3-oxazines can be hydrolysed to the corresponding ethylenic aminoalcohols by heating with hydrochloric acid.

Introduction

Since the discovery in 1966 that carbon alkylation of ambident anions by p-nitrobenzyl chloride or 2-halo-2-nitropropanes is an electron-transfer chain process in which radical anions and free radicals are intermediates,[1] these transformations termed $S_{RN}1$ reactions,[2] have been studied extensively.[3-8] A most attractive feature of these reactions is that they proceed under very mild conditions and produce excellent yields of pure products. As a consequence, they are especially valuable for the synthesis of a large number of complex and highly branched compounds. Substitution proceeding by an $S_{RN}1$ mechanism at sp^3 carbons attached to heterocyclic systems has not been as widely studied as in the benzene and alkane series. Reactions with derivatives of pyridines, quinolines, nitrothiophenes, nitrofurans, nitroimidazoles and imidazoles have been reported.[9] With few exceptions the nucleophiles used with these systems are restricted to anions of simple secondary nitroalkanes.

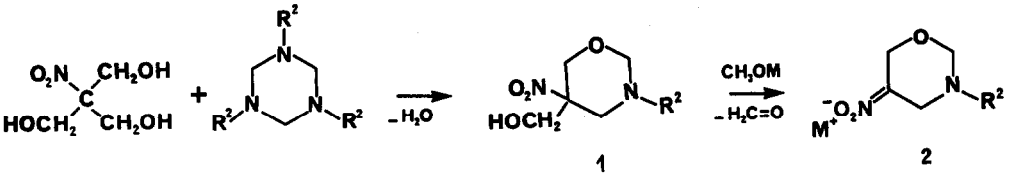
In connection with allied studies[10] including structure-reactivity-activity relationship deduction, we are exploring the reactivity and synthetic usefulness of various nitro heterocyclic salts with additional features (anion delocalization, internal nucleophile, steric hindrance,...) in $S_{RN}1$ reactions [11] with a view toward drug discovery.

† Dedicated to the memory of Professor Tadeuz URBANSKI, a pioneer in the chemistry of nitro compounds.

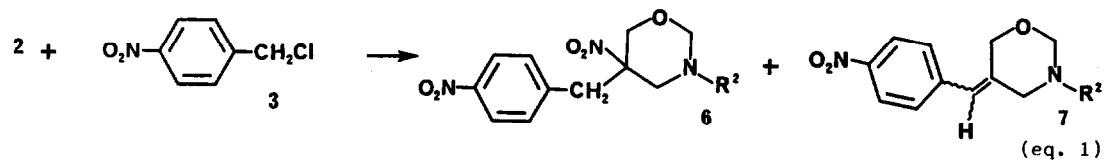
Many tetrahydro-1,3-oxazine derivatives with a nitro group at the 5 position have been prepared and their chemistry has been reviewed by Urbanski.[12] Because of its easy preparation the nitronate anion 2 appeared to be a good candidate to initiate a study of the reactivity of heterocyclic nitronates in typical $S_{RN}1$ reactions. This paper reports the results of the reaction of three representive substrates, p-nitrobenzyl chloride (3), 2,2-dinitropropane (4) and 1-methyl-2-chloromethyl-5-nitroimidazole (5) with 2 under different experimental conditions.

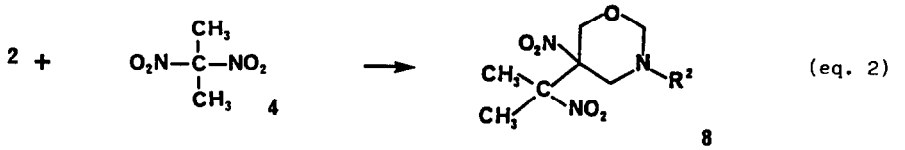
Results and discussion

Compound 1 (R = CH_2CH_3) was prepared by the method[13] described previously from 2-hydroxymethyl-2-nitro-1,3-propanediol and 1,3,5-triethylhexahydro-s-triazine. Treatment of 1 with sodium or lithium methoxide split off formaldehyde to give the corresponding salt 2.



Under an inert atmosphere at room temperature, 2 reacts cleanly with 3, 4 and 5, respectively, as indicated in the following equations (eq. 1,2,3).
Results of the different experiments are collected in Table 1.





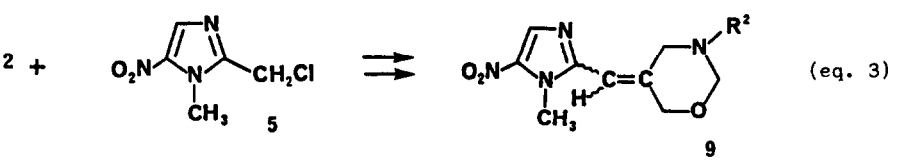


Table 1

Formation of 3-ethyltetrahydro-1,3-oxazines in the reactions of 2[a,b]

Mole equiv. of 2	Solvent	Electrophile	6	7[c]	8	9[c]	Total Yield(%)
1	MeOH	3	63	6			69
1[d]	MeOH	3	54	6			60
2	MeOH	3	15	69			84
2[e]	MeOH	3	37	50			87
3	MeOH	3	5	78			83
1	DMF	3	56	6			62
1	DMSO	3	56	6			62
2[e]	DMSO	4			64		64[f]
2[d,e]	DMSO	4			30		30[f]
2	MeOH	5				90	90

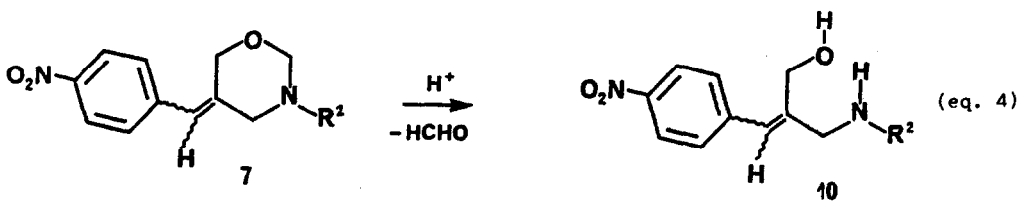
(a) Unless otherwise noted, all reactions were performed for 24h under argon with the sodium salt of 2 (b) Products as per cent of theoritical yield relative to the electrophile as pure isolated products. (c) Isomers 7 and 9 : Z to E ratio of 1/1. (d) The system is exposed to the light of two ordinary 60-W fluorescent lamps. (e) Li^+ is the counterion. (f) After 48 hours.

The results reported in Table 1 show that reaction of the sodium (or lithium) salt 2 with p-nitrobenzyl chloride in MeOH, DMF or DMSO produced a good yield of 3-ethyl-5-p-nitrobenzyl-5-nitrotetrahydro-1,3-oxazine (6). As expected, the heterocyclic nitronate anion 2 reacts with 3 to give the C-alkylation product 6 in agreement with an $S_{RN}1$ mechanism. The reaction is accelerated by the illumination with a fluorescent light, but the yield of 6 is lowered with the formation of an increased quantity of resinous products. The same unfavourable effect of light on yield was observed in the reaction of 2 with 4. It is not clear at this stage how irradiation leads to the formation of resinous products. However, it is known that irradiation with U.V. light can reduce the time for ring opening of 5-nitrotetrahydro-1,3-oxazines by acid hydrolysis.[12] Also even when sun-light is excluded, intramolecular charge-transfer complexes with 5-nitro derivatives of hexahydropyrimidines can be detected by ESR.[14] Some results indicate that 6 also gives ESR signals.[14] This ability to form charge-transfer complexes which can lead to fragmentation products may explain the light-promoted by-products. This observation led us to perform other reactions without fluorescent illumination. Electron-transfer substitution also occurs with amines[4] and the formation of a quaternary ammonium salt is possible. Nevertheless, quaternary ammonium salts are good leaving groups in $S_{RN}1$ reactions and these hidden electrophiles, if involved, would not change the final products. Unsaturated compounds 7 formed from 6 by the elimination of nitrous acid became major products when 2 was in excess. A significant influence of the counterion is observed in this case, sodium being more effective than lithium for nitrous acid elimination. We have shown elsewhere[11] that 6 in

C_6H_6 treated with 1.5 equivalent of 40% NBu_4OH in water at room temperature gave **7** in near quantitative yield. This result confirms that nitrous acid elimination is base-promoted. In the case of imidazole **5**, the fact that the methylene group at the 2 position is activated by the nitro heterocyclic system and the tertiary nitro group is on a cyclic carbon permits the formation of **9** in high yields. For **7** and **9**, the Z and E isomers are present in a ratio of 1:1 as determined by ^1H NMR and are easily separated by chromatography.

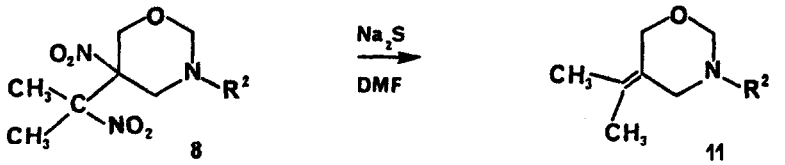
Tetrahydro-1,3-oxazine derivatives have attracted much attention owing to the fact that these compounds show interesting biological activity and are used as chemotherapeutic agents.[15]

From a synthetic point of view, an attractive property of 5-nitro tetrahydro-1,3-oxazines is their hydrolytic ring opening.[16] This method of preparing 3-amino-2-nitropropanols is the best known procedure of a general character.[17] The most universal method of hydrolysis currently used consists of heating the oxazines with concentrated hydrochloric acid diluted with ethanol to a concentration of 1-1.5%. This method gives an almost quantitative yield of the corresponding 2-substituted 3-amino-2-nitro-propanols. Formaldehyde, which is evolved in the course of the reaction, can be removed by distillation with alcohol. This reaction has been extended to the ring opening of the mixture of 3-ethyl-5-p-nitrobenzylidene-tetrahydro-1,3-oxazines (**7**) (eq. 4) which gives the corresponding aminoalcohols **10** in 96% yield.



(eq. 4)

The unsymmetrical vicinal dinitro compound **8** obtained by the displacement of a nitro group from 2,2-dinitropropane by salt **2** was easily converted to tetrasubstituted olefin **11** by elimination of two nitro groups. This reaction first described by Kornblum [18] is a result of the elimination of two nitro groups from a vicinal dinitro compound by the action of sodium sulfide in DMF.



(eq. 5)

3-Ethyl-5-isopropylidene-tetrahydro-1,3-oxazine (**11**) is formed in good yield (eq. 5) and this reaction can be used to prepare new tetrahydro-1,3-oxazines with tetrasubstituted double bonds in the 5 position.

Conclusions

In this investigation, both novel and well-established methods for the synthesis of new tetrahydro-1,3-oxazine derivatives have been explored. The reactions of the

heterocyclic nitronate anion **2** with p-nitrobenzyl chloride, 2,2-dinitropropane and 1-methyl-2-chloromethyl-5-nitroimidazole demonstrate the ability of this heterocyclic nitronate anion to react by an $S_{RN}1$ mechanism. 5-Substituted-5-nitro tetrahydro-1,3-oxazines have been obtained in good yields and the finding that 5-nitrotetrahydro-1,3-oxazine salts react smoothly by an $S_{RN}1$ mechanism suggests that a wide variety of heterocyclic nitronate anions will provide new substituted heterocycles which were previously very difficult to prepare. The base-promoted nitrous acid elimination, which is relatively easy when the tertiary nitro group is bonded to a cyclic carbon atom, offers a useful new approach to tetrahydro-1,3-oxazines with a trisubstituted double bond at the 5 position. By varying the nature of the electrophile, a variety of other structures may be realized. Vicinal dinitro compounds obtained from 2,2-dinitropropane and 5-nitro tetrahydro-1,3-oxazine lithium salt, treated by sodium sulfide follows the known chain process and affords tetrahydro-1,3-oxazines with a tetrasubstituted double bond at the 5 position. Finally, it has been demonstrated in one example that acid hydrolysis of a tetrahydro-1,3-oxazine with a trisubstituted double bond at the 5 position is a good method for the preparation of a 2-p-nitrobenzylidene-3-aminopropan-1-ols.

In conclusion, by using the reactivity of 5-nitrotetrahydro-1,3-oxazines, it is possible to prepare in good yields new tetrahydro-1,3-oxazines with tri- or tetrasubstituted double bonds at the 5 position and by acid hydrolysis the corresponding ring opened 3-aminopropanols.

Experimental

Melting points were determined with a Buchi apparatus in capillary tubes and are uncorrected. Column chromatography was carried out on Merck silica gel 60 (0.063-0.2 mm). The ^{1}H-NMR were recorded on a Varian EM 360 or XL 200 spectrometer. Chemical shifts are reported in δ units (ppm) relative to internal TMS. A Ribermag R.10.10 C spectrometer was used to obtain the mass spectra. Microanalyses were performed at the Ecole de Chimie de Marseille.

p-Nitrobenzyl chloride, 2-hydroxymethyl-2-nitropropane-1,3-diol and 1,3,5-triethylhexahydro-s-triazine purchased from Janssen, Fluka and Aldrich, respectively, were used as obtained.

3-Ethyl-5-hydroxymethyl-5-nitrotetrahydro-1,3-oxazine **(1)** was prepared from 2-hydroxymethyl-2-nitropropane-1,3-diol and 1,3,5-triethylhexahydro-s-triazine by the known procedure[13] and purified by crystallization from benzene (m.p. 65°C) : ^{1}H NMR ($CDCl_3$) δ 1.1 (t,3H), 2.5 (q,2H), 2.7-4.8 (m,8H), 3.4 (s,1H). Calcd. for $C_7H_{14}N_2O_4$: C, 44.20 ; H, 7.42 ; N, 14.73. Found : C, 44.21 ; H, 7.34 ; N, 14.56.

2,2-Dinitropropane (4) was prepared according to the method described earlier[19] m.p. 35-36°C : ^{1}H NMR ($CDCl_3$) δ 2.20(s).

1-Methyl-2-chloromethyl-5-nitroimidazole (5) was obtained as reported elsewhere[10] : m.p. 42°C ; ^{1}H NMR ($CDCl_3$) δ 4.0 (s,3H), 4.6 (s,2H), 7.86 (s,1H).

General Procedure for Preparation of 3-Ethyl-5 nitrotetrahydro-1,3-oxazine salts and their Reactions with p-Nitrobenzyl chloride, 2,2-Dinitropropane and 1-Methyl-2-chloromethyl -5-nitro-imidazole.

Compound **1** (7.6g, 0.04 mol) was mixed with a 6% methanolic solution of sodium (0,92 g, 0.04 g atom), warmed to 40° on a water bath for 30 min, and cooled. p-Nitrobenzyl chloride (**3**) (3.43 g, 0.02 mole) in 60 ml of methanol was added over 30 min. The reaction was allowed to proceed for 24 hr at room temperature under an inert atmosphere. After about 1 hr, a white precipitate began to appear. After 24 hr, methanol was distilled off on a rotatory evaporator under reduced pressure and 100 ml of water was added to the residue which was extracted with chloroform. The extracts were dried and evaporated to give a residual oil which was purified by column chromatography (SiO_2), using a mixture $CHCl_3/Et_2O$ (6:4) as eluent. The process was the same with lithium. For reactions in solvents other than methanol, the methanol was removed on a rotatory evaporator under reduced pressure and the resulting slurry was subjected to vacuum for 30 min, crushed and kept under vacuum (5.10^{-4} Torr) for 1 hr. The resulting solid was dissolved in DMF or DMSO and the electrophile in solution in the same solvent was dropped over 30 min. After 24 hr, the solution was added to 200 ml of water and extracted with three 100 ml portions of benzene and one of ether. The combined organic layers were dried over magnesium sulphate and concentrated. For reactions in the presence of light, two ordinary 60W lamps were placed on opposite sides 10 cm from the flask. To maintain room temperature, the flask was cooled with compressed air.

3-Ethyl-5-p-nitrobenzyl-5-nitrotetrahydro-1,3-oxazine (6) was purified by crystallization from ethanol : m.p. 114°C ; ^{1}H NMR ($CDCl_3$) δ 1.07 (t,3H), 2.52 (q,2H), 3.17 (m,2H), 3.3 (s,2H), 4.03 (m,2H), 4.16 (s,2H), 7.2 (d,2H), 8.13 (d,2H). Calcd. for $C_{13}H_{17}N_3O_5$: C, 52.88 ; H, 5.80 ; N, 14.23. Found : C, 52.88 ; H, 5.81 ; N, 13.88.

3-Ethyl-5-p-nitrobenzylidene-tetrahydro-1,3-oxazine (7)

The two isomers were separated by chromatography (hexane/ethyl acetate 18:6) on silica gel. The first isomer eluted **7** Z is a pale yellow solid which was purified by crystallization from ethanol/water 6:4 : m.p. 99°C ; ^{1}H NMR ($CDCl_3$) δ 0.9 (t,3H), 2.65 (q,2H), 3,75 (s,2H), 4.35 (s,2H), 4.53 (s,2H), 6.55 (s,1H), 7.33 (d,2H), 8.2 (d,2H). Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89 ; H, 6.50 ; N, 11.28. Found : C, 62.83 ; H, 6.50 ; N, 11.26.

The second isomer eluted **7** E is a pale brown oil : ^{1}H NMR ($CDCl_3$) δ 1.1 (t,3H), 2.75 (q,2H), 3.7 (s,2H), 4.52 (s,4H), 6.42 (s,1H), 7.28 (d,2H), 8.18 (d,2H).

3-Ethyl-5-(2-nitroisopropyl)-5-nitrotetrahydro-1,3-oxazine (8) was purified by crystalliza -tion from ethanol : m.p. 81°C ; ^{1}H NMR ($CDCl_3$) δ 1.05 (t,3H), 1.7 (s,6H), 2.5 (q,2H), 2.8-4.1 (m,4H), 4.2-5 (m,2H). Calcd. for $C_9H_{17}N_3O_5$: C, 43.72 ; H, 6.93 ; N, 16.99. Found : C, 43.77 ; H, 6.98 ; N, 16.92.

1-Methyl-2-(3-ethyl-tetrahydro-1,3-oxazine 5-ylidenemethyl)-5-nitroimidazole (9)

The two isomers were separated by chromatography (hexane/ethyl acetate 18:6) on silica gel. Isomer **9** E is a yellow solid which was recrystallized from cyclohexane : m.p. 113°C ; ^{1}H NMR ($CDCl_3$) δ 1.13 (t,3H), 2.76 (q,2H), 3.66 (s,2H), 3.96 (s,3H), 4.5 (s,2H), 4.9 (s,2H), 6.06 (s,1H), 8.0 (s,1H). Calcd. for $C_{11}H_{16}N_4O_3$: C, 52.37 ; H, 6.39 ; N, 22.21. Found : C, 52.32

; H, 6.47 ; N, 22.20.

The second isomer **9** Z was eluted as a brown oil : ^{1}H NMR ($CDCl_3$) δ 1.07 (t,3H), 2.71 (q,2H), 4.00 (s,3H), 4.22 (s,2H), 4.40 (s,2H), 4.55 (s,2H), 6.25 (s,1H), 8.02 (s,1H).

2-p-Nitrobenzylidene-3-ethylamino-propanol (10)

A mixture of isomers **6** (0.01 mol, 2.48 g) was dissolved in ethanol (45 ml) in a three-necked flask provided with a still-head, a condenser, and a dropping funnel. Water (8 ml) and concentrated hydrochloric acid (2 ml) were added. The resulting solution was boiled for 5 hr with collecting of ethanol (50 ml) as a distillate. The level in the flask was maintained by adding ethanol (50 ml) and water (8 ml) through the dropping funnel. After evaporation under reduced pressure and cooling, the hydrochloride is suspended in ether (80 ml) and shaken with saturated sodium bicarbonate (60 ml) until the hydrochloride dissolved. The ether layer was washed with water, dried over sodium sulphate. Removal of the solvent furnished the base as a yellow solid 2.26g (96%) which was purified by crystallization from ethanol : m.p. 127°C ; ^{1}H NMR ($CDCl_3$) δ 1.1 (t,3H), 2.64 (q,2H), 3.16 (s,2H), 3.54 (s,2H), 4.38 (s,2H), 6.64 (s,1H), 7.32 (d,2H), 8.18 (d,2H). Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00 ; H, 6.83 ; N, 11.86. Found : C, 61.01 ; H, 6.86 ; N, 11.87.

The E and Z isomers are not distinguished by ^{1}H NMR spectrum.

3-Ethyl-5-isopropylidene-tetrahydro-1,3-oxazine (11)

A stirred mixture of **8** (2.25g, 0.0089 mol) and Na_2S, $9H_2O$ (5.4g, 0.0225 mol) in 50 ml of DMF under nitrogen was exposed to room light for 48 hr. The olefin **11** was isolated by pouring the reaction mixture into water, extracting with pentane, washing with water,drying over anhydrous $MgSO_4$ and removing the solvent to give 0.75g (54%) of **11** : b.p. 79-82°C (7.5 mm Hg) ; ^{1}H NMR ($CDCl_3$) δ 1.1 (t,3H), 1.7 (s,6H), 2.67 (q,2H), 3.5 (s,2H), 4.32 (s,2H), 4.40 (s,2H) ; Mass : m/e 155(M^+, 34.6), 140(53.3), 124(15.4), 110(50.3), 96(6.0), 79(10.7), 67(19.6), 58(100), 41(58.4), 30(10.8).

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