ALKYLATION OF CYCLIC GEM-DINITROSAMINES

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Abstract - Alkylations with benzaldehyde catalyzed by potassium tert-butoxide converted 1,3,5-trinitrosohexahydro-1,3,5-triazine 1, 1,3-dinitrosoimidazolidine 3 and 1,3-dinitrosohexahydropyrimidine 4 to the 2-hydroxybenzyl derivatives (76 - 88%) and, in one instance, to the dialkylated product, 2,4-di-(hydroxybenzyl)-1,3,5-trinitrosohexahydro-1,3,5-triazine (40%). Lithium diisopropylamide was a less effective catalyst in alkylations with benzaldehyde or methyl iodide and was converted to diisopropylnitrosamine by transnitrosation. A catalytic amount of triethylbenzylammonium chloride promoted efficient mono-α-benzylations of nitrosamines 3 and 4 in aqueous sodium hydroxide at 25°C; however, simple nitrosamines failed to react and the trinitrosamine 1 was decomposed by the alkaline medium.

We wish to report the first examples of α-alkylation of polynitrosamines.[1] The project was undertaken in a search for ways to incorporate functional C-substituents in 1,3,5-trinitrosohexahydro-1,3,5-triazine 1 for oxidation to derivatives of 1,3,5-trinitrohexahydro-1,3,5-triazine 2 (RDX).

Both 1,3-dinitrosoimidazolidine 3 and 1,3-dinitroshexahydropyrimidine 4 were readily converted to 2-alkyl derivatives. In tetrahydrofuran (THF) at -78°C potassium t-butoxide catalyzed alkylations with benzaldehyde to give the hydroxybenzyl derivatives 5 (88%) and 6 (76%). Attempts to alkylate further the dinitrosamines 5 and 6 in reactions with benzaldehyde and potassium t-butoxide at temperatures from -78° to -60°C were unsuccessful; the starting materials 5 and 6 were nearly quantitatively recovered. Lithium diisopropylamine (LDA) was less effective in a reaction (-80°C) with benzaldehyde to give the product 5 (42%). It also promoted a similar reaction with methyl iodide to give 2-methyl-1,3-dinitrosoimidazolidine 7 (60%). Instead of catalyzing methylation or benzylation of the dinitrosamine 4

LDA (-80°C) underwent transnitrosation to N-nitrosodiisopropylamine 8 (20%).[5]

Efficient benzylations of the dinitrosamines 3 and 4 were brought about at 25°C in a phase transfer reaction with benzyl bromide in sodium hydroxide (50%) containing triethylbenzylammonium chloride. After 12 h 2-benzyl-1,3-dinitrosoimidazolidine 9 (79%) and 2-benzyl-1,3-dinitrosohexahydropyrimidine 10 (50%) were obtained. The latter yield was raised to 75% when two moles of benzyl bromide were initially present. Attempts to alkylate simple mononitrosamines in similar phase transfer reactions were unsuccessful.

Instead of promoting alkylations of the trinitrosamine 1, LDA underwent transnitrosation to the nitrosamine 8; the best yield of 8 (80%) was obtained from an excess of LDA (3.3 equivalents) at -80°C in the absence of an alkylating agent. The trinitrosamine 1 proved to be an efficient transnitrosating agent toward amine anions; the highly hindered lithium 2,2,6,6-tetramethylpiperidide[6] was converted (40%) to the nitrosamine 11.[7]

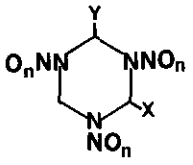
Sodium hydroxide solutions slowly dissolved the trinitrosamine 1 with an evolution of an ammoniacal odor indicating ring degradation. At room temperature the trinitrosamine was unaffected by either sodium or potassium hydride but decomposition on heating with sodium hydride was slow, faster with potassium hydride.

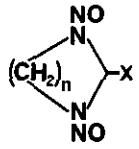
Alkoxides catalyzed mono- and dialkylation of the trinitrosamine 1 with benzaldehyde to give 2-hydroxybenzyl- 12 and 2,4-dihydroxybenzyl-1,3,5-trinitrosohexahydro-1,3,5-triazine 13. Potassium t-butoxide at -80°C afforded the monoalkylation product 12 (79%) and in a separate operation catalyzed the conversion of the latter to the dialkylated product 13 (40%). The assignment as a 2,4-disubstituted derivative 13 rather than a 2,2-disubstituted isomer is tentative. It was supported by examples in which axial but not equatorial hydrogen at an adjacent carbon atom was replaced by an alkyl group in similar reactions with cyclic mononitrosamines.[8] Also the replacement of only one hydrogen (presumably axial) at C-2 in the dinitrosamines 3 and 4 was noted. An unresolved complexity of ^{1}H and ^{13}C nmr spectra was partially attributed to the presence of geometrical nitrosamine isomers.[9]

Attempts to further alkylate compound 13 with benzaldehyde at low temperatures under the catalysis of potassium t-butoxide led to the recovery of compound 13 (75%). At higher temperatures complex mixtures were obtained as shown by tlc. Reversibility[10] of the alkylation with benzaldehyde was demonstrated by treatment of product 12 in t-butyl alcohol with a catalytic amount of potassium t-butoxide at 25°C to give benzaldehyde, identified by nmr and the dinitrophenylhydrazone

derivative, and the trinitrosamine 1.

Attempts to achieve other base catalyzed reactions between the trinitrosamine 1 and methyl iodide, ethyl iodide, benzyl bromide, formaldehyde, n-propyl nitrite, p-toluenesulfonylazide, and O-methylhydroxylamine were unsuccessful.





1 n = 1, X = Y = H

2 n = 2, X = Y = H

12 n = 1, X = $CH(OH)C_6H_5$, Y = H

13 n = 1, X = Y = $CH(OH)C_6H_5$

3 n = 2, X = H

4 n = 3, X = H

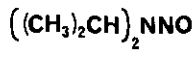
5 n = 2, X = $CH(OH)C_6H_5$

6 n = 3, X = $CH(OH)C_6H_5$

7 n = 2, X = CH_3

9 n = 2, X = $CH_2C_6H_5$

10 n = 3, X = $CH_2C_2H_5$



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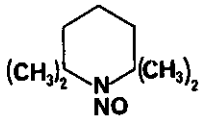

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EXPERIMENTAL

Preparations of 1,3,5-trinitroso-1,3,5-triazine 1,[9] and 1,3-dinitrosohexahydropyrimidine 4[11] followed literature procedures. Instruments included spectrometers: Pye-Unicam ir SP200, and Hewlett-Packard GCMS 5985. Elemental analyses were provided by Micro-Tech Laboratories, Skokie, Illinois.

1,3-Dinitrosoimidazolidine 3. *To a mixture of ethylenediamine* (30.0 g, 0.50 mol) and aqueous formaldehyde (37.5 g, 0.50 mol) prepared and stored at 0°C for 2 h a solution of sodium nitrite (69.0 g, 1.0 mol) in water (200 ml) and sulfuric acid (26%, 235 ml) were added simultaneously as the temperature was kept below 5°C. After the mixture was stirred at 5°C for 1 h the product 3 was separated as a light yellow solid (20.0 g, 31%) mp 38-40°C after purification by recrystallization from a mixture of ether and petroleum ether; ir (KBr): 1440 cm^{-1} (NO). Anal. calcd. for $C_3H_6N_4O_2$: C, 27.70; H, 4.65; N, 43.06; found: C, 27.56; H, 4.71; N, 43.11.

2-Hydroxybenzyl-1,3-dinitrosoimidazolidine 5 .- To LDA (0.59 g, 5.5 mmol) in THF

(40 ml) at -90°C 1,3-dinitrosoimidazolidine 3 (0.65 g, 5.0 mmol) in THF (5 ml) followed by benzaldehyde (0.53 g, 5.0 mmol) were added and the mixture was stirred for 3 h. Acetic acid (0.33 g, 5.5 mmol) was added and the solution was allowed to warm to 25°C. THF was removed by evaporation and the residue dissolved in methylene chloride (50 ml) was washed with a saturated solution of sodium chloride, dried, and evaporated to give the product 5 as a yellow gum which became a yellow solid (0.50 g, 42%), mp 87-90°C after recrystallization from a mixture of ether and petroleum ether. Ir (KBr): 3380 (OH), 1440 cm^{-1} (NO); m/e (70 eV): 237 $(M+1)^+$ (2%), 206 $(M-30)^+$ (1%), 79 $(C_6H_7)^+$ (100%) Anal. Calcd for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.76; H, 5.10; N, 23.74.

2-Methyl-1,3-dinitrosoimidazolidine 7. A similar procedure gave the product 7 as a yellow oil (60% yield) purified by pot to pot short path distillation (bath temperature 110-130°C, 0.1 Hg mm). Ir (thin film): 1440 cm^{-1} (NO); m/e (70 eV): 144 M^+ (2%), 114 (7%), 70 (100%). Anal. calcd for $C_4H_8N_4O_2$: C, 33.33; H, 5.59; N, 38.81. Found: C, 33.69; H, 5.54; N, 38.37.

2-Hydroxybenzyl-1,3-dinitrosoimidazolidine 5. A mixture of 1,3-dinitrosoimidazolidine (0.65 g, 5.0 mmol) and benzaldehyde (0.53 g, 5.0 mmol) in THF (5 ml) was added to potassium t-butoxide (0.56 g, 5.0 mmol) in THF (50 ml) at -78°C and the mixture was held at this temperature for 2 h. After workup as described above the product 5 was obtained as a light yellow solid (1.04 g, 88%), mp 86-90°C. A tlc analysis and ir analysis showed the product to be identical with the sample previously obtained.

2-Hydroxybenzyl-1,3-dinitrosohexahydropyrimidine 6. A similar procedure gave the product as a yellow gum (76%). Treatment with acetic anhydride gave the acetate ester derivative as a yellow solid, mp 110-114°C after recrystallization from ether. Ir (KBr): 1750 (CO), 1450 cm^{-1} (NO). Anal. calcd for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.36; H, 5.58; N, 19.21.

2-Benzyl-1,3-dinitrosoimidazolidine 9. A mixture of 1,3-dinitrosoimidazolidine 3 (0.65 g, 5.0 mmol), benzyl bromide (0.86 g, 5.0 mmol), and a catalytic amount of benzyltriethylammonium chloride in sodium hydroxide (50%, 5 ml) was stirred for 16 h, diluted with water (25 ml), and extracted with ether (2 x 25 ml). The organic layer was washed with water, dried, and evaporated to leave the product 9 as a yellow viscous oil (0.87 g, 79%) which solidified on standing and gave a mp 70-72°C after recrystallization from a mixture of ether and petroleum ether. Ir (KBr): 1450 cm^{-1} (NO); m/e (70 eV): 220 M^+ (0.07%), 91 (100%). Anal. calcd for

$C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.64; H, 5.56; N, 25.33.

2-Benzyl-1,3-dinitrosohexahydropyrimidine 10. - A similar procedure with two equivalents of benzyl bromide gave the product 10 (75%) as a yellow viscous oil. Ir (thin film): 1450 cm^{-1} (NO); m/e (70 eV): 235 $(M+1)^+$ (0.1%), 91 (100%) Anal. calcd for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.49; H, 6.07; N, 23.69.

2-Hydroxybenzyl-1,3,5-trinitrosohexahydro-1,3,5-triazine 12. - A mixture of 1,3-5-trinitrosohexahydro-1,3,5-triazine 1 (0.87 g, 5.0 mmol) and benzaldehyde (0.53 g, 5.0 mmol) was added to potassium t-butoxide (0.56 g, 5.0 mmol) in THF (50 ml) at -78°C and stirred at this temperature for two hours. Acetic acid (0.30 g, 5.0 mmol) was added and the mixture was warmed to 25°C. THF was removed by evaporation and the residue dissolved in methylene chloride (50 ml) was washed with a saturated solution of sodium chloride, dried, and evaporated to give the product 12 as a light yellow solid (1.10g, 79%), mp 123-126°C after recrystallization from a mixture of ether and petroleum ether. Ir(KBr): 3450 (OH) and 1500 cm^{-1} (NO); m/e (70 eV): 281 $(M+1)^+$ (0.13%), 107 (100%). Anal calcd. for $C_{10}H_{12}N_6O_4$: C, 42.86; H, 4.28; N, 30.00. Found: C, 43.00; H, 4.27; N, 30.31.

2,4-Di(hydroxybenzyl)-1,3,5-trinitrosohexahydro-1,3,5-triazine 13. - In a similar reaction the monoalkylated trinitrosamine 12 was stirred at -78°C for three hours and stored at -60°C for 2 h before proceeding as described above to give a mixture after washing with a saturated solution of sodium chloride, drying, and removing methylene chloride by evaporation. The crude mixture was applied to a silica gel column. Methylene chloride eluted unreacted benzaldehyde (40%) and the trinitrosamine 12 (29%). Further elution gave the product 13 (40%) as a light yellow gum which became a powder, mp 166-169°C after trituration with a mixture of ether and petroleum ether. Recrystallization from a mixture of ether and petroleum ether gave a yellow solid, mp 170-174°C. Ir(KBr): 3450 (OH) and 1500 cm^{-1} (NO); m/e (70 eV): 107 (100%). Anal. calcd for $C_{17}H_{18}N_6O_5$: C, 52.85; H, 4.70; N, 21.75. Found: C, 53.23; H, 5.10; N, 21.89.

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