Reduction of 4-Methyl-1,2,4-triazin-5(4*H*)-ones with Sodium Borohydride. Regioselective Preparation of Dihydro-1,2,4-triazin-5(4*H*)-ones [1]

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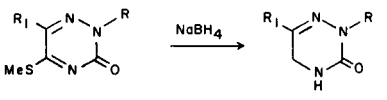
Received September 30, 1983

Reduction of 3-methylthio-1,2,4-triazin-5(4*H*)-one (**1a**) with sodium borohydride afforded 3-methylthio-1,6-dihydrotriazin-5(4*H*)-one (**2b**) selectively. 3-Methylthio-6-*t*-butyl-1,2,4-triazin-5(4*H*)-one (**1d**) reacted with sodium borohydride to give mainly 6-*t*-butyl-2,3-dihydro-1,2,4-triazin-5(4*H*)-one (**3d**). The reaction of various 4-methyl-1,2,4-triazin-5(4*H*)-ones with sodium borohydride and the influence of bulkiness and electronic effect of the substituents at the 3- and 6-positions upon the product ratio, are also discussed.

J. Heterocyclic Chem., **21**, 639 (1984).

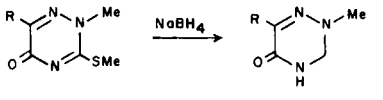
In some recent studies on the reductive demethylthiolation of 5-methylthio-1,2,4-triazin-3(2*H*)-ones and 3-methylthio-1,2,4-triazin-5(2*H*)-ones, we discovered an interesting method for the synthesis of dihydro-1,2,4-triazinones [2,3] (Scheme I).

Scheme I



R = H, Me

R_1 = H, Me, i-Pr, Ph

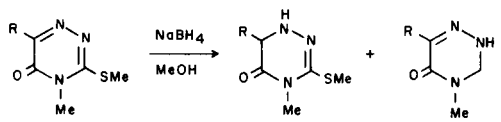


R = H, Ph, t-Bu

Extension of these works induced us to explore the reaction of 4-methyl-1,2,4-triazin-5(4*H*)-ones with sodium borohydride. In this paper, we discuss the regioselective preparation of 1,6-dihydro-1,2,4-triazin-5(4*H*)-ones and 2,3-dihydro-1,2,4-triazin-5(4*H*)-ones by the reaction of 4-methyl-1,2,4-triazin-5(4*H*)-ones with sodium borohydride.

Firstly, the reduction of 3-methylthio-4-methyl-1,2,4-triazin-5(4*H*)-ones **1a-d** [4] possessing the various substituents at the 6-position was attempted. Treatment of 3-methylthio-1,2,4-triazin-5(4*H*)-one (**1b**) with one equivalent of sodium borohydride in methanol for 30 minutes at room temperature resulted in the unexpected formation of 3-methylthio-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (**2b**) in 51% yield together with 2,3-dihydro-1,2,4-triazin-5(4*H*)-one (**3b**) in 11% yield (Scheme II). The structure of a

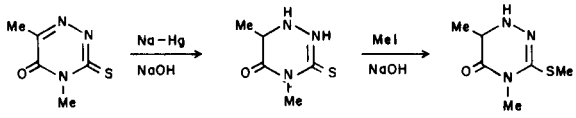
Scheme II



a, R = H b, R = Me c, R = i-Pr d, R = t-Bu e, R = Ph

novel heterocyclic compound **2b** was elucidated on the basis of spectroscopic and alternative synthetic studies. Its ir spectrum gave an absorption at 1690 cm^{-1} indicating the existence of a carbonyl group. The pmr spectrum of **2b** in deuteriochloroform exhibits a broad resonance signal at δ, 5.30 due to the N-H proton which is distinguished by addition of deuterium oxide. Methyl protons at the 6-position, split into a doublet by the adjacent H-6 proton, appear at δ, 1.32, indicating a characteristic structure of 1,6-dihydrotriazinone. On the other hand, sodium-amalgum reduction of 3-thio-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**4**) gave 3-thio-1,6-dihydro-1,2,4-triazinedione (**5**) in 31% yield. *S*-Methylation of **5** with methyl iodide provided 3-methylthio-4-methyl-1,6-dihydrotriazin-5(4*H*)-one which was identical in all respects with **2b** described above. Compound **3b** was found to be identical with an authentic

Scheme III



4 5 2b

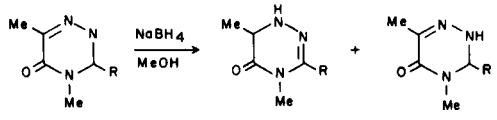
sample of 4,6-dimethyl-2,3-dihydro-1,2,4-triazin-5(4*H*)-one obtained by the reaction of 4,6-dimethyl-1,2,4-triazin-5(4*H*)-one and lithium aluminium hydride [5].

Similar reduction of 3-methylthio-4-methyl-1,2,4-triazin-5(4*H*)-ones was examined and the results are summarized in Table I. These results suggest that the bulkiness at the 6-position has a large influence on the ratio of the 1,6-dihydro-1,2,4-triazinones to the 2,3-dihydro-1,2,4-triazinones. Reduction of **1a** (R = H) with sodium borohydride gave only 1,6-dihydro-1,2,4-triazinone (**2a**) which was too labile to be fully characterized. In the case of **1d** (R = *t*-Bu), 2,3-dihydro-1,2,4-triazinone (**3d**) was regioselectively obtained in 71% yield.

In order to examine the substituent effect at the 3-position of 4-methyl-1,2,4-triazinones toward sodium boro-

hydride reduction, we investigated several 3-substituted 1,2,4-triazin-5(4*H*)-ones **6a-c** [6]. Similar reduction of 4,6-dimethyl-1,2,4-triazin-5(4*H*)-one (**6a**) afforded a mixture of two products, 1,6-dihydrotriazinone **7a** and 2,3-dihydrotriazinone **3b**, in 13% and 71% yield, respectively, while 3,4,6-trimethyl-1,2,4-triazin-5(4*H*)-one (**6b**) gave 1,6-dihydrotriazinone **7b** and 2,3-dihydrotriazinone **8b**, 21% and 67% yield, respectively. These results show that the steric effect at the 3-position also control the nucleophilic

Scheme IV



6a, R = H
6b, R = Me
6c, R = Ph

7a, R = H
7b, R = Me
7c, R = Ph

3a, R = H
8b, R = Me

orientation of sodium borohydride. However, the large difference between methylthio- and methyl groups at the 3-position (compare, for example **1b** and **6b**) indicates that the electronic effect is also involved in determining the relative rate of the competing reaction. The presence of methylthio group at the 3-position makes it unfavorable to attack the position 3 by hydride anion due to inductive effect. In each case of **1e** and **6c** (R = Ph), 2,3-dihydro-1,2,4-triazinone **2e** and 1,6-dihydro-1,2,4-triazinone **7c** were regioselectively gained in 82% and 95% yield, respectively, thus indicating the presence of the electronic effect of the phenyl group.

It is thus possible to prepare regioselectively 1,6- and 2,3-dihydrotriazinones by the reaction of 1,2,4-triazin-5(4*H*)-ones with sodium borohydride. Further, it is concluded that both the bulkiness and the electronic effects of the substituents at the 3- and 6-positions control the nucleophilic orientation of sodium borohydride.

Table I

Reductions of 3-Methylthio-1,2,4-triazin-5(4*H*)-ones **1a-e** with Sodium Borohydride

Compound	R	Yield 2 (%)	Yield 3 (%)
1a	H	96	0
1b	Me	51	11
1c	i-Pr	34	15
1d	t-Bu	0	71
1e	Ph	0	82

Table II

Reductions of 4,6-Dimethyl-1,2,4-triazin-5(4*H*)-ones **6a-c** with Sodium Borohydride

Compound	R	Yield 7 (%)	Yield 8 (%)
6a	H	13	71 [a]
6b	Me	21	67
6c	Ph	95	0

[a] The product was **3b**.

Table III

Analytical and Spectral Data of 1,6-Dihydro-1,2,4-triazinones

Compound	Mp °C [a]	Molecular Formular	Analysis % Calcd./(Found) C	H	N	Ms M^+	IR, cm^{-1} (C=O) [b]	PMR (δ ppm) (Deuteriochloroform)
2a	oil	$C_5H_9N_3OS$	37.73 (—)	5.70 (—)	29.36 (—)	159	1685	2.22 (s, 3H, SCH_3), 3.17 (s, 3H, 4-CH_3), 3.48 (s, 2H, CH_2), 5.52-5.92 (br s, 1H, NH)
2b	94	$C_6H_{11}N_3OS$	41.61 (41.46)	6.40 (6.38)	24.27 (24.11)	173	1690	1.32 (d, 3H, 6-CH_3), 2.37 (s, 3H, SCH_3), 3.18 (s, 3H, 4-CH_3), 3.28-3.57 (m, 1H, H6)
2c	101	$C_8H_{15}N_3OS$	47.75 (47.64)	7.51 (7.47)	20.88 (20.72)	201	1690	1.02 (d, 6H, $(CH_3)_2C$-), 1.24-1.35 (m, 1H, $(CH_3)_2CH$), 2.39 (s, 3H, SCH_3), 3.22 (s, 3H, 4-CH_3), 3.22-3.38 (m, 1H, H6)
7a	66	$C_5H_9N_3O$	47.23 (47.08)	7.13 (7.16)	33.05 (32.84)	127	1670	1.38 (d, 3H, 6-CH_3), 3.06 (s, 3H, 4-CH_3), 3.53 (q, 1H, H6), 6.61 (s, 1H, H3)
7b	oil	$C_6H_{11}N_3O$	51.04 (51.09)	7.86 (7.59)	29.77 (29.60)	141	1670	1.37 (d, 3H, 6-CH_3), 2.16 (s, 3H, 3-CH_3), 3.18 (s, 3H, 4-CH_3), 3.49 (q, 1H, H6)
7c	168	$C_{11}H_{12}N_3O$	65.33 (65.42)	5.97 (5.68)	20.77 (20.57)	203	1690	1.39 (d, 3H, 6-CH_3), 3.00 (s, 3H, 4-CH_3), 3.30-3.70 (m, 1H, H6), 7.35 (s, 5H, aromatic)

[a] From isopropyl alcohol-*n*-hexane. [b] In nujol.

Table IV

Analytical and Spectral Data of 2,3-Dihydro-1,2,4-triazinones

Compound	Mp °C [a]	Molecular Formular	Analysis % Calcd./(Found) C	H	N	MS M^+	IR, cm^{-1} (C=O) [d]	PMR (δ ppm) (Deuteriochloroform)
3a	oil [b]	$C_5H_9N_3O$	47.23 (47.43)	7.13 (7.40)	33.05 (33.21)	127		
3b	79 [c] (A)	$C_6H_{11}N_3O$	51.04 (51.01)	7.86 (7.90)	29.77 (29.51)	141	1670	1.46 (d, 3H, 3-CH_3), 2.07 (s, 3H, 6-CH_3), 2.96 (s, 3H, 4-CH_3), 4.67 (q, 1H, H3)
3c	oil	$C_7H_{13}N_3O$	54.17 (54.08)	8.44 (8.68)	27.08 (26.88)	155	1670	1.12 (d, 6H, $(CH_3)_2$C-), 2.98 (s, 3H, 4-CH_3), 3.15 (q, 1H, $(CH_3)_2$C*H*), 4.38 (s, 2H, CH_2)
3d	101 (B)	$C_8H_{15}N_3O$	56.78 (56.66)	8.94 (9.24)	24.83 (24.73)	169	1675	1.28 (s, 9H, *t*-butyl), 2.96 (s, 3H, 4-CH_3), 4.34 (s, 2H, CH_2)
3e	149 (B)	$C_{10}H_{11}N_3O$	63.48 (63.39)	5.86 (5.82)	22.21 (22.07)	189	1670	2.95 (s, 3H, 4-CH_3), 4.30 (s, 2H, CH_2), 7.12-7.80 (m, 5H, aromatic)

[a] Recrystallization solvents: A = *n*-hexane, B = isopropyl alcohol. [b] Lit [5]. [c] Lit [5] oil. [d] In nujol.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary melting apparatus and are uncorrected. The ^1H nmr spectra were recorded on a Hitachi R-900 spectrometer operating at 90 MHz as an internal standard. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6M instrument equipped with a solid sample injector; the ionizing voltage was 70 eV. The ir spectra were recorded on a Hitachi 260-10 spectrometer.

General Procedure for Preparation of Dihydro-1,2,4-triazinones, **2a-c** and **3b-e**.

3-Methylthio-4-methyl-1,2,4-triazin-5(4*H*)-ones, **1a-e** (3 mmoles) were dissolved in dry methanol (30 ml) and sodium borohydride (3 mmoles) was added portionwise at room temperature. The reaction mixture was stirred at room temperature for 0.5-6 hours, then the solvent was evaporated *in vacuo*. After cooling, water was added and neutralized with glacial acetic acid. The product was extracted with chloroform, washed with water and then dried over anhydrous sodium sulfate. The crude oily product obtained by removal of chloroform *in vacuo* was subjected to silica gel column chromatography. Elution with *n*-hexane-acetone (4:1) gave purified compounds **2a-e** and **3b-e**. Physical properties of these compounds are given in Table III and IV.

3-Thio-4,6-dimethyl-1,6-dihydro-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**5**).

To a solution of 0.8 g (5.1 mmoles) of 3-thio-4,6-dimethyl-1,2,4-triazine-3,5-dione (**4**) and 0.3 g (7.5 mmoles) of sodium hydroxide in 10 ml of water was added 5 g of 5% sodium-amalgam at 0°. The mixture was stirred for 0.5 hour. After the water layer was decanted, the solution was neutralized with glacial acetic acid the crude product was collected and recrystallized from ethanol affording 0.24 g (31%) of an analytical sample **5**, mp 184°; pmr (DMSO-d_6): 1.18 (d, 3H, 4-CH_3), 3.30 (s, 3H, 6-CH_3), 3.09-3.35 (m, 1H, H6), 5.65-6.05 (m, 1H, NH).

Anal. Calcd. for $C_5H_9N_3OS$: C, 37.73; H, 5.70; N, 26.41. Found: C, 37.78; H, 5.86; N, 26.45.

3-Methylthio-4,6-dimethyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (**2b**).

To a solution of 1.0 g (6.3 mmoles) of 2-thio-4,6-dimethyl-1,2,4-triazinedione (**5**) and 0.3 g (7.5 mmoles) of sodium hydroxide in 20 ml of water added at 0°. 1.2 g (8.0 mmoles) of methyl iodide. After the reaction mixture was stirred at room temperature for 4 hours, the solution was neutralized with dilute hydrochloric acid and the product extracted with chloroform. The chloroform extracts were combined, dried over magnesium sulphate, filtered and the solvent removed. The 3-methylthio-1,6-dihydro-1,2,4-triazinone (**2b**) (0.8 g, 74%) was obtained as a white solid, mp 94°, after recrystallization from isopropyl alcohol-*n*-hexane; the pmr, ir and mixture melting point indicated that this heterocycle was identical with **2b** obtained by the reaction of 3-methylthio-1,2,4-triazin-5(4*H*)-one (**1b**) with sodium borohydride.

General Procedure for Preparation of Dihydro-1,2,4-triazinones, **7a-c**, **3b**, and **8b**.

4,6-Dimethyl-1,2,4-triazin-5(4*H*)-ones **6a-c** (3.0 mmoles) were dssolved in dry methanol (30 ml) and sodium borohydride (3.0 mmoles) was added portionwise at room temperature. The reaction mixture was stirred at room temperature for 3 hours, then the solvent was evaporated *in vacuo*. After cooling, water was added and neutralized with glacial acetic acid. The product was extracted with chloroform, washed with water and then dried over anhydrous sodium sulfate. The crude oily product obtained by removal of chloroform *in vacuo* was subjected to silica gel column chromatography. Elution with chloroform-methanol (50:1) gave purified compounds **7a-c**, **3b** and **8b**. Physical properties of these compounds are given in Table III and IV.

REFERENCES AND NOTES

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