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REDUCTION OF ISOTHIOCYANATES TO THIOFORMAMIDES WITH TRI–n–BUTYLTIN HYDRIDE

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Summary: Thioformamides have been prepared from isothiocyanates and tri–*n*–butyltin hydride under mild conditions with high yield.

Organotin hydrides are useful intermediates in organic synthesis[1]. The reaction of triphenyltin hydride with arylisocyanates gave corresponding formamides[2]. However, the analogous transformation of isothiocyanates into thioformamides has received very little attention[3,4]. Only, Noltes and Janssen[5] identified *N*–phenylthioformamide as a minor product (2%) in the addition of triethyltin hydride to phenylisothiocyanate. The formation of isocyanides[2,6], amines[2], and hydrocarbons[6] by the reaction of isothiocyanates with organotin hydrides has been published. In this context, Witczak[7] has recently reported the desulphurization of glycosylisothiocyanates with tri–*n*–butyltin hydride. In the presence of AIBN this reaction led to 1,5–anhydroalditoles *via* isolable intermediate isocyanides. The absence of AIBN favoured the formation of glycosylisocyanides.

We have observed that thioformamides are initially formed in the reductions of isothiocyanates with tri–n–butyltin hydride depending upon conditions. Thus, when the reactions were carried out with two mol of hydride, isothiocyanates **1**–**6**[8] were converted into the corresponding thioformamide derivatives **7**–**12**[9] as only products, except in the case of the partially protected galactopyranosyl isothiocyanate **5** that also afforded the bicycle thiocarbamate **13** as a minor product (Table 1, entries 1–7). In addition, when the amount of tri–n–butyltin hydride was limited (entries 9 and 10) **7** was newly obtained and the excess of **1** could be recovered (entry 9).

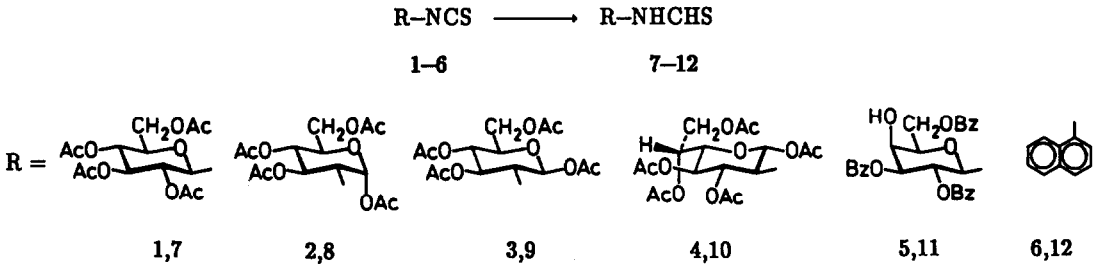
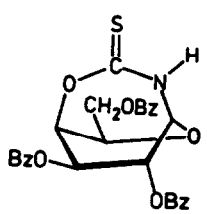


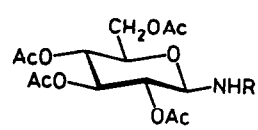
Table 1. Experimental conditions for preparations of 7–15[a]

Entry	Subst.	[Bu_3SnH]/[subst] in mol	Solv.	Time in h	Initiator or inhibitor (gx100/g of subst.)	Compound isolated (yield)
1	1	2.0	ether	6		7 (87)
2	1	2.0	toluene	6	AIBN (10)	7 (60)
3	2	2.0	ether	6		8 (82)
4	3	2.0	ether	6		9 (65)
5	4	2.0	ether	6		10 (89)
6	5	2.0	ether	6		11(44) and 13 (9)
7	6	2.0	ether	144		12 (56)
8	1	1.5	ether	24		7 (54)
9	1	1.0	ether	6	AIBN (6)	7 (48) and 1 (11)
10	1	1.0	ether[b]	6		7 (45) and 1[c]
11	1	2.0	ether	72	hidroquinone (6)	7[c] and 1 (50)
12	1	4.0	ether	120	AIBN (12)	14[c] and 15 (11)
13	1	6.0	toluene	109	AIBN (10)	14 (15) and 15 (10)
14	5	4.0	ether	48		11 (11) and 13 (15)
15	7	4.0	toluene	2	AIBN (10)	14 (21)

[a] At 25° except for entry 15 that was performed under reflux. [b] Humidified with D_2O. [c]Observed by t.l.c. in the end of the reaction, but not isolated.



13



14 R=CH_3

15 R=CS–OMe

Alternatively, when the reaction was performed with an excess of hydride (entries 12 and 13) **1** was also transformed (observed by t.l.c.) into **7** that evolved gradually to a complex mixture of compounds from which **14** and unexpectedly, **15**[10] could be isolated. The *N*–methylglucosylamine **14** was also isolated from the mother liquors of the reduction of **7** (entry 15).

The reactions were carried out under inert atmosphere (argon or nitrogen), monitored by t.l.c. and i.r., and the isolation of the products was performed by column chromatography or crystallization after elimination of tin residues by washing the acetonitrile solution of the crude product with light petroleum.

On the other hand, in the presence of AIBN, the formation of the thioformamide occurred more readily (t.l.c.), and the addition of hidroquinone inhibited the reduction of **1** (entry 11). In addition, when the reaction was performed in ethyl ether slightly humidified with D_2O (entry 10), undeuterated **7** (tested by MS) was obtained, thus discarding the hydrolytic formation of the C–H bond[5]. The above results suggest a free–radical mechanism, in agreement with the course of many organotin hydride reactions[1].

^{1}H– and ^{13}C–NMR of **7**–**12**[9] showed signals due to the *Z*– and *E*–isomers in a sequence related to the one observed in the formamide series[11].

In conclusion, in this report we give an account of a new synthesis of thioformamides under mild conditions. In these reductions, the isonitriles[6,7] have not been isolated or detected. The application of this reaction to the field of carbohydrates is of particular interest because valuable and formerly unknown sugar thioformamides have been prepared. The scope and limitations of this synthesis and the use of these new thioformamides as starting materials in nucleoside preparation is now under study in our laboratory.

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9. Data for **7**: M.p. 144–146°, $[\alpha]_D$ +50° (4 h, *c* 0.5, $CHCl_3$); ^{1}H–NMR data (200 MHz, $CDCl_3$): *Z*–isomer δ 8.40–8.60 (m, 1H, NH), 9.52 (d, J = 5.3 Hz, 1H, CHS); *E*–isomer δ 8.60–8.40 (m, 1H, NH), 9.40 (d, J = 13.8 Hz, 1H, CHS); MS (EI, 70eV) m/z 391 ($M^{\cdot+}$, 13%), 331 (17), 43 (100). Data for **8**: M.p. 178–179°; $[\alpha]_D$ +48° (24 h, *c* 0.5, $CHCl_3$); ^{1}H–NMR data (200 MHz, $CDCl_3$): *Z*–isomer δ 8.08 (dd, J = 5.9, 7.9 Hz, 1H, NH), 9.40 (d, J = 5.9 Hz, 1H, CHS); *E*–isomer 7.88–8.18 (m, 1H, NH), 9.20 (d, J = 13.9 Hz, 1H, CHS). Data for **9**: Higroscopic solid, $[\alpha]_D$ –31° (2 h, *c* 0.5, $CHCl_3$); ^{1}H–NMR data (200 MHz, $CDCl_3$): *Z*–isomer δ 8.35 (dd, J = 6.2, 9.2, 1H, NH), 9.50 (d, J = 6.1 Hz, 1H, CHS); *E*–isomer δ 8.53 (dd, J = 9.9, 14.0 Hz, 1H, NH), 9.18 (d, J = 14.0 Hz, 1H, CHS). Data for **10**: M.p. 206–207°; $[\alpha]_D$ +65° (24 h, *c* 0.5, $CHCl_3$); ^{1}H–NMR data (200 MHz, $CDCl_3$): *Z*–isomer δ 7.95 (dd, J = 6.0, 7.8 Hz, 1H, NH), 9.49 (d, J = 6.0 Hz, 1H, CHS); *E*–isomer δ 8.21 (dd, J = 11.2, 13.7 Hz, 1H, NH), 9.17 (d, J = 13.7 Hz, 1H, CHS). Data for **11**: M.p. 103–106°; $[\alpha]_D$ +123° (3 h, *c* 0.5, $CHCl_3$); ^{1}H–NMR data (200 MHz, $CDCl_3$): *Z*–isomer δ 9.13–9.30 (m, 1H, NH), 9.57 (d, J = 5.0 Hz, 1H, CHS); *E*–isomer δ 9.13–9.30 (m, 1H, NH), 9.51 (d, 1H, CHS). Data for **12**: M.p. 149–151°; ^{1}H–NMR data (200 MHz, DMSO–d_6): *Z*–isomer δ 9.81 (d, J = 6.1 Hz, 1H, CHS), 12.07 (bs, 1H, NH); *E*–isomer δ 9.79 (d, J = 13.6 Hz, 1H, CHS), 12.58 (d, J = 13.6 Hz, 1H, NH).

10. Compound **15** was unequivocally synthesized by addition of methanol to **1**.

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