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NUCLEOPHILIC CLEAVAGE OF N-SUBSTITUTED -3- OXO- 2,3- DIHYDRO BENZO (d) - 1,2 -THIAZOLE-1,1-DIOXIDE WITH HYDRAZINE HYDRATE

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ABSTRACT

The reaction profile of certain 2-substituted-3-oxo-2,3- dihydrobenzo (d)-1,2- thiazole-1,1-dioxide (N-substitued saccharines) with hydrazine hydrate is described. It was found that the steric hindrance displayed by the substituents at position-2 has a profound effect on reaction rate. Some of the synthesized compounds were subjected to priliminary antimicrobial activity.

INTRODUCTION

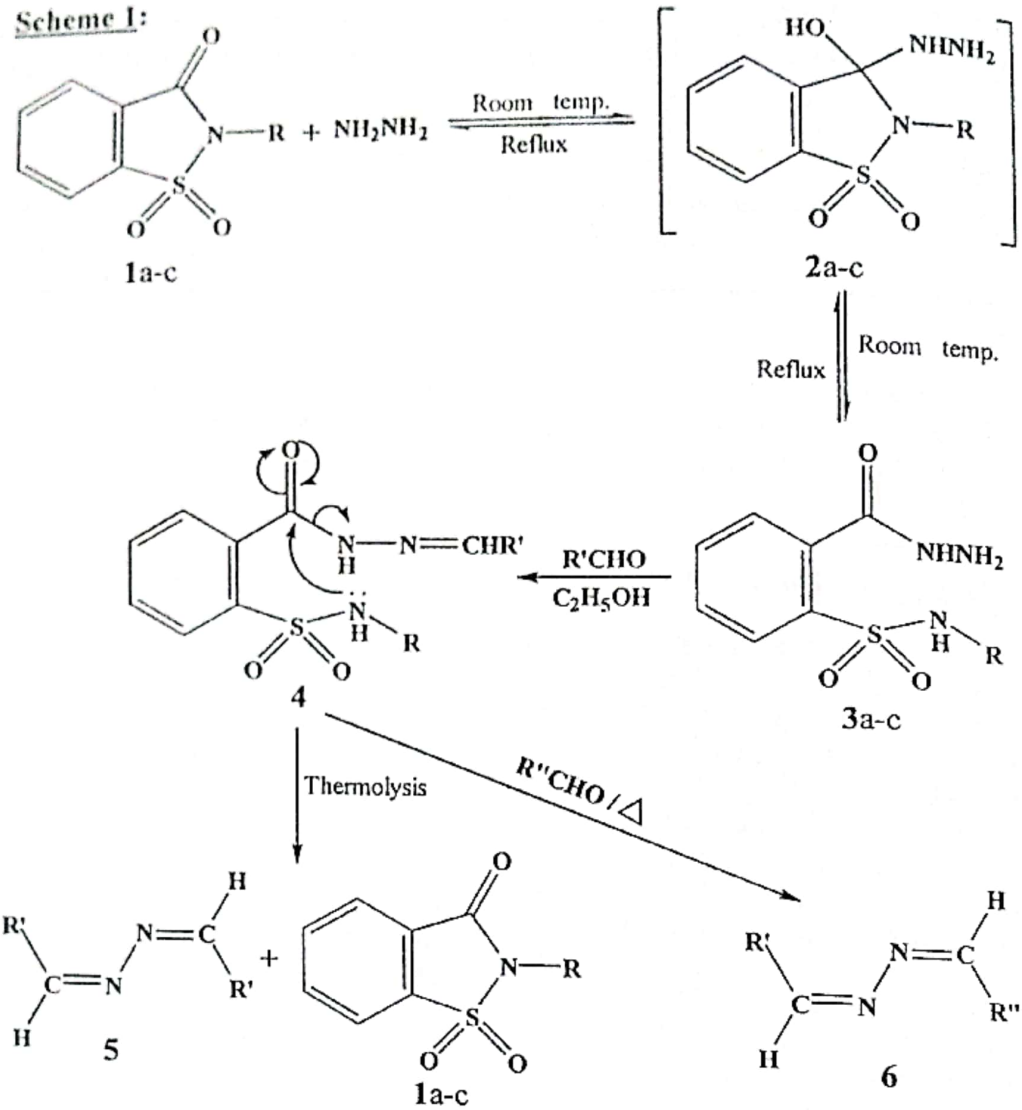
Hydrazinolysis of compound **1a** has been reported to give via the intermediate **2a**, an orthodiamide (**Scheme 1**). The reaction was proved to be reversible and product **3a** was only performed by adjusting the reaction temperature to 0°C in absence of solvent. Attempted heating of the reactions led to unsatisfactory results. Consequently, this work is extended to explore the effect of various parameters including time, temperature, and particularly the steric and electronic effects of the carbon residue at position 2 on the rate of hydrazinolysis. In addition, special interest was devoted to explain the unexpected chemical behaviour of these compounds when reacted with hydrazine hydrate compared to N-substituted phthalimides. The key starting materials **1a-c** namely, N-ethyl, N-isopropyl, and N-benzyl saccharines were prepared from saccharin sodium by alkylation (1) using the appropriate alkyl halide. Treating **1a-c** with hydrazine hydrate afforded the corresponding ortho-disubstituted amide rather than the expected benzo-1,2,3-thiadiazine pathway B (Scheme 2).

Formation of ortho-disubstitued amides **3a-c** is also proceeded via two step reversible reaction as previously reported(2). This reversibility made it possible to get either **1a-c** or 3a-c via the intermediate 2a-c depending on the energy barriers on both sides. Thus, product 3a was obtained in fairly good yield upon performing the reaction neat on cold, while 3b,c were obtained at higher temperature in refluxing ethanol. This variation in reaction conditions is principally attributed to the steric hindrance displayed by the alkyl residue at position 2.

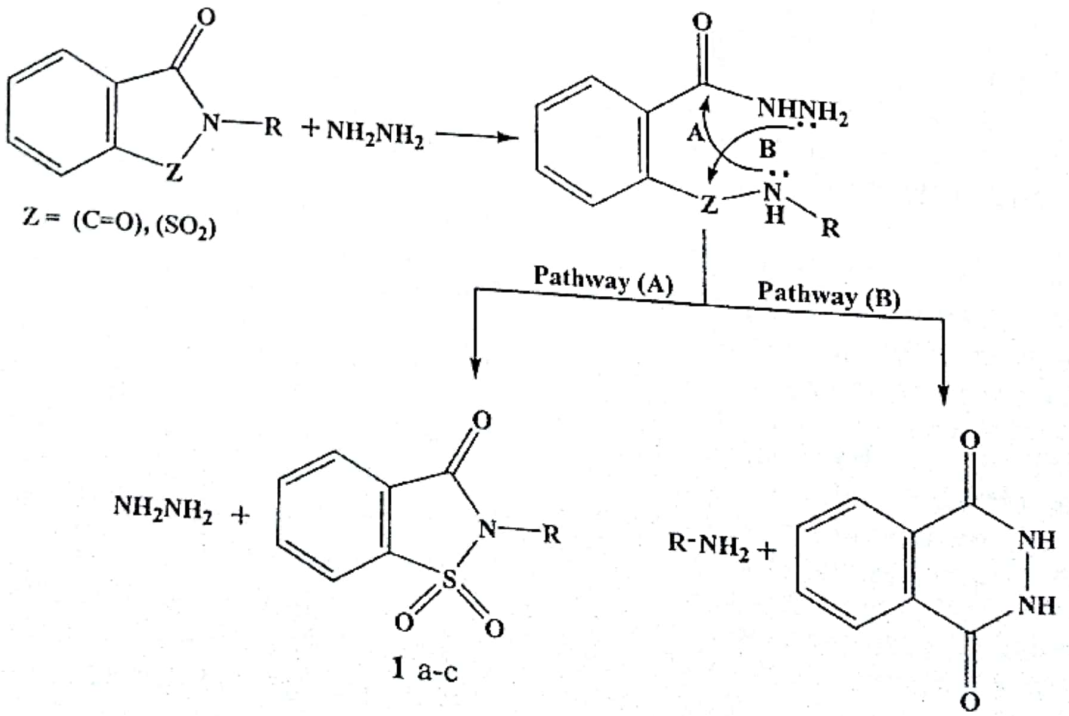
Reaction progress was monitored by TLC technique. It was revealed that the time elapsed to attain the final ortho-disubstituted amides was 5 min., 1.5 and 2.5 hrs. corresponding to the products **3a, 3b**, and **3c**, respectively. Thus, N-ethyl saccharin proved to be the best N-substituted saccharin to undergo hydrazinolytic cleavage both due to milder condition and shorter reaction time (5 min.).This is attributable to the minor steric interaction of the relatively small-sized ethyl grouping, which permits maximum interaction with hydrazine hydrate. Steric effect of the N-substituted residue became apparent in case of N-isopropyl and N-benzyl saccharines leading to sluggish reaction rates and higher temperature (refluxing ethanol). In parallel, thermolysis of the ortho-disubstituted amides 4 resulted in reversed intramolecular nucleophilic cyclization to give **1a-c** along with the corresponding symmetrical azines **5**.(3) However, performing similar condition in the presence of other carbonyl compounds yielded the asymmetric azines **6** as previously reported(4,5) . It worth mentioning the rate of thermolysis of **1a-c** are quite identical which provides further evidence on the participation of steric hindrance displayed by (R) group. Thus, thermolysis of compound **4 c** showed the slowest cyclization rate due to shielding of the nucleophilicity of sulphamoyl nitrogen by the large bulky group R=$(CH_3)_2CH$-, ($C_6H_5CH_2$). On the other hand, compound 4a is readily cyclized to 1a since the nitrogen is less exposed to steric impedance of the least bulky alkyl group (R = C_2H_5).

Theoretically, thermolysis of ortho -disubstituted amides where Z (SO_2 or C=O) might undergo intramolecular cyclization

Scheme 1:



Scheme 2:



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either through pathway (A) to give **(1a-c)** or pathway (B) to afford phthalazinedione with expulsion of the amine. The latter pathway is the famous Gabriel phthalimide reaction.(6) Substituting C=O by the bioisoster SO_2 group resulted in unusual intramolecular cyclization via pathway (A) to give N-substituted saccharin.

This anomalous behaviour can be explained on the basis of nucleophilic property of acid hydrazide and sulphamoyl nitrogens. Under basic condition, the sulphamoyl nitrogen loses hydrogen proton to form nitranion which undergoes cyclization via pathway (A) to give N-substituted saccharin. It was noticed also that the rate of cyclization is affected by adjacent substituent due to the free rotation of these substituents, which hinder the nitranion from reaching to reaction site. On the contrary, the hydrazide nitrogen is more nucleophilic than amide carbonyl, hence cyclization takes place through pathway (B).

EXPERIMENTAL

All melting points were uncorrected and were determined using Gallenkamp apparatus. Elemental analyses were carried out at the microanalytical center of Cairo University. IR spectra were taken on a Pye Unicam LTD, Cambridge, England. 1H-NMR spectra were carried out on EM-390, 90 MHz spectrometer. Mass spectra were determined using HP model MS-5988 spectrometer.

N-substituted-3-oxo-2,3-dihydrobenzo(d)-1, 2-thiazole-1,1-dioxides (1b and 1c):

To a solution of saccharin sodium (0.1 mol) in dimethylformamide (15 ml), the appropriate alkyl halide (0.1 mol) was added. The reaction was maintained at 100°C for 2 hrs. it was then cooled and diluted with water. The obtained product was crystallized from aqueous ethanol.

N-(isopropyl) saccharin (1b1); yield 80%, m.p 114°C. Analysis for ($C_{10}H_{11}NO_3S$) calcd: C, 53.31; H, 4.92; N, 6.22. Found: C, 53.20; H, 4.95; N, 6.10. m/z 251 (M+, 4.72%), 149 (34.58%), 129 (39.53%), 81.05 (66.4%), 89.05 (100%, base peak). IR (cm-1): 3250 (NH), 3040 (CH arom.), 2910 (CH aliph.), 1675 (CONH), 1620 (C=C).

N-benzyl) saccharin (1c); yield 90%, m.p 57°C. Analysis for ($C_{14}H_{11}NO_3S$) calcd: C, 61.52; H, 6.59; N, 8.32. Found: C, 61.48; H, 6.43; N, 8.21. IR (cm-1): 3240 (NH), 3070 (CH arom.), 2890 (CH aliph.), 1665 (CONH, 1620 (C=C).

2-(Substituted aminosulfamoyl) benzoic acid hydrazides (3b, 3c):

To a solution of **1b,c** (0.01 mol) in absolute ethanol (15 ml), hydrazine hydrate 99% (0.03 ml) was added. It was heated under reflux for the required time (1.5 and 2.5 hrs for **1b** and **1c**, respectively). The solution was concentrated under reduced pressure, diluted with water and extracted with $CHCl_3$. The chloroformic extract was dried over anhydrous Na_2SO_4 and filtered. Pet. ether (10 ml) was added while stirring to give the pure products. Compound **2c** was separated as oily product while compound **3b** was separated as solid which was crystallized from ethanol.

Compound 3b: yield 70%, m.p 218°C. Analysis for ($C_{10}H_{15}N_3O_3S$) calcd: C, 46.68; H, 5.87; N, 16.33. Found: C, 46.40; H, 6.01; N, 16.36. IR (cm-1): 3200-3300 (NH, NH_2), 3020 (CH arom.), 2880 (CH aliph.), 1640 (CONH), 1620 (C=C), 1550 (SO_2NH). ($C_{10}H_{15}N_3O_3S$) requires 257.292. m/z: 257 (M+, 4.72%), 149 (34.58%), 129 (39.83%), 81.05 (66.4%), 89.05 (100%, base peak).

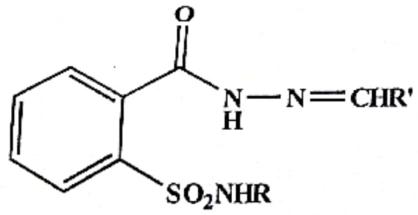
2-(N-substituted aminosulfonyl) benzoic acid hydrazones (4a1-5, 4b1-9):

A mixture of **3b** and **3c** (0.01 mol) and the appropriate carbonyl compound (0.01 mol) in ethanol, was stirred at room temperature for 2 hrs; the sticky viscous substance obtained was stirred with pet. ether, then the solid substance produced was filtered and recrystallized from ethanol (Table 1).

Microbiological Evaluation:

Hydrazones are reported to have antimicrobial properties (7-9) . This motivated the authors to subject the newly developed hydrazones to biological studies aiming at finding derivatives of improved activity since the latter hydrazones bear a non classical sulphonamide moiety in their structures. Some selected hydrazones **4 a, b, d, f** were screened for their appropriate antimicrobial activity using the cup plate method. It was found that all compounds have significant activity against gram-negative bacteria compared to sulphacetamide (Table 2).

Table 1: *Arylidene 2-(N-substitutedaminosulfonyl)* benzoic acid hydrazides



Comp.	R	R'	m.p °C	Yield %	Molecular Formula	Analysis		IR(cm^{-1})			
						Calcd.	Found	C=O	S=O	NH	NO
$4b_1$	$CH(Me)_2$	p-$(OH)C_6H_4$	245-7	80	$C_{17}H_{19}N_3O_4S$	C=56.50 H=5.29 N=11.63	56.36 5.32 11.50	1665	1300	3420	-
$4b_2$	$CH(Me)_2$	p-$(NO_2)C_6H_4$	215-7	80	$C_{17}H_{18}N_4O_5S$	C=52.30 H=4.65 N=14.35	52.12 4.50 14.20	1680	1320	3440	1350
$4b_3$	$CH(Me)_2$	m-$(NO_2)C_6H_4$	213-5	85	$C_{17}H_{18}N_4O_5S$	C= 52.30 H= 4.65 N= 14.35	52.12 4.50 14.20	1680	1310	3430	1340
$4b_4$	$CH(Me)_2$	p-$(Cl)C_6H_4$	208-9	80	$C_{17}H_{18}N_3O_3SCl$	C= 59.24 H= 5.27 N= 12.20	59.40 5.35 12.35	1680	1340	3440	-
$4b_5$	$CH(Me)_2$	p-$(Me_2N)C_6H_4$	210-11	75	$C_{22}H_{21}N_3O_4S$	C= 62.40 H= 4.99 N= 9.92	62.05 4.81 9.75	1660	1330	3400	-
$4c_1$	C_7H_7	p-$(OH)C_6H_4$	180-2	85	$C_{21}H_{17}N_3O_3S$	C= 64.43 H= 4.37 N= 10.73	64.20 4.43 10.61	1670	1340	3490	
$4c_2$	C_7H_7	p-$(Cl)C_6H_4$	170-2	85	$C_{21}H_{18}N_3O_3SCl$	C= 58.30 H= 4.20 N= 9.81	58.50 4.32 9.95	1665	1320	3420	-

Table 1: (Continue)

Comp.	R	R'	m.p °C	Yield %	Molecular Formula	Analysis		IR(cm^{-1})			
						Calcd.	Found	C=O	S=O	NH	NO
$4c_3$	C_7H_5	o-(Cl)C_6H_4	140-2	80	$C_{21}H_{18}N_3O_3SCl$	C= 58.30 H= 4.20 N= 9.81	58.50 4.32 9.59	1660	1330	3420	-
$4c_4$	C_7H_5	m-(Cl)C_6H_4	160-2	80	$C_{21}H_{18}N_3O_3SCl$	C= 58.30 H= 4.20 N= 9.81	58.50 4.32 9.59	1670	1340	3420	-
$4c_5$	C_7H_5	p-(NO_2)C_6H_4	170-2	85	$C_{21}H_{18}N_4O_5S$	C= 57.53 H= 4.14 N= 12.78	57.34 4.30 12.62	1660	1310	3430	1340
$4c_6$	C_7H_5	m-(NO_2)C_6H_4	160-2	80	$C_{21}H_{18}N_4O_5S$	C= 57.53 H= 4.14 N= 12.78	57.34 4.30 12.62	1680	1280	3420	1350
$4c_7$	C_7H_5	o-(NO_2)C_6H_4	155-7	80	$C_{21}H_{18}N_4O_5S$	C= 57.53 H= 4.14 N= 12.78	57.34 4.30 12.62	1650	1350	3420	1350
$4c_8$	C_7H_5	p-(Me_2N)C_6H_4	170-1	85	$C_{23}H_{24}N_4O_3S$	C= 63.29 H= 5.54 N= 12.83	63.50 5.62 12.71	1680	1320	3400	-
$4c_9$	C_7H_5	p-(MeO)C_6H_4	172-3	85	$C_{22}H_{21}N_3O_4S$	C= 62.40 H= 4.99 N= 9.92	62.10 4.85 9.50	1650	1400	3440	-

Compound $4c_2$: m/z 427 (M^+, 27.32%), 353.2 (40.95%), 222.05 (12.689), 220 (15.12%), 185.95 (5.37%), 1883 (6.34%), 78 (100%).

Compound $4b_1$: ^{1}H-NMR 2.75 (6H, d, $2CH_3$), 3.35 (1H, br, m, NH-CH_2-C_4), 6.9, 7.65 (4H, dd, $1.5H_2$, $2.5H_2$ of p-disusbstitution), 7.85-8.05 (4H, m, ArH).

Compound $4c_1$: ^{1}H-NMR 7.02 (5H, br, m, CH-C_6H_5), 7.85 (5H, m, CH_2-C_6H_5), 8.3 (1H, s, N=CH), 11.1 (1H, br, CONH), 14.85 (1H, br, s, SO_2NH).

Table 2: The antimicrobial activity of the selected hydrazones

Compound	Zone of inhibition (mm) after 24 hrs incubation				
	Staph. aureus	*B. subtilis*	*Neisseria spp*	*E. coli*	*C. albicans*
4_{c7}	-	5	17	10	-
4_{c9}	7	7	16	15	-
4_{c3}	5	5	15	10	-
4_{b5}	5	3	10	15	-
sulphacetamide	20	-	10	20	-

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