Nickel Boride Mediated Reductive Desulfurization of 2-Thioxo-4(3*H*)-quinazolinones: A New Synthesis of Quinazolin-4(3*H*)-ones and 2,3-Dihydro-4(1*H*)-quinazolinones

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A novel one-pot approach for the synthesis of aryl substituted quinazolin-4(3*H*)-ones and 2,3-dihydro-4(1*H*)-quinazolinones has been reported based on the reductive desulfurization of 3-aryl-2-thioxo-4(3*H*)-quinazolinones with nickel boride in dry methanol at ambient temperature.

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The sedative-hypnotic (neurotoxic) antiviral and anticancer properties, of compounds possessing quinazolinone ring system are well documented [1], which provides additional impetus for the development of new synthetic approaches for substituted quinazolin-4(3*H*)-one and 2,3-dihydro-4(1*H*)-quinazolinone derivatives. Among the diverse synthetic methods [2] for the synthesis of compounds having a 4(3*H*)-quinazolinone ring system, Niementowski reaction and its modifications, involving the condensation between anthranilic acid or esters and amides, amidines or amines [3] is of considerable importance. The yields are generally around 50%. Cyclocondensation of anthranilic acid, formic acid (or orthoesters) and an amine under microwave irradiation [4] is also reported. Apart from Niementowski approach, amminolysis of 3,1(4*H*)-benzoxazin-4-ones has also drawn attention in recent times [5] for the synthesis of complex quinazolin-4(3*H*)-ones.

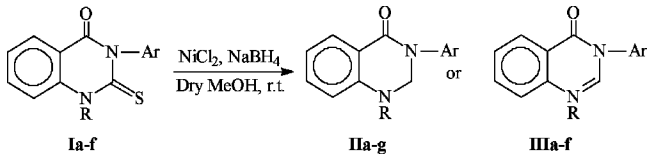
Unlike a variety of methods available for the synthesis of quinazolin-4(3*H*)-ones, the synthesis of 2,3-dihydro-4(1*H*)-quinazolinones [6] has not received much attention despite the fact that a number of compounds of this category are also known for their pharmaceutical importance. Hence there is sufficient scope for the development of new, efficient and more practical protocols for the syntheses of these two important classes of quinazoline derivatives. In view of our experience with nickel boride as a reducing agent [7] and as a dethiating agent for compounds containing C=S group [8], we decided to explore its potential to achieve reductive desulfurization of 3-aryl-2-thioxo-4(3*H*)-quinazolinones so as to provide a new and alternative route for the syntheses of various aryl substituted quinazolin-4(3*H*)-ones and 2,3-dihydro-4(1*H*)-quinazolinone derivatives.

Results and Discussion.

We report herein a convenient and efficient synthesis of 2,3-dihydro-4(1*H*)-quinazolinones (**IIa-g**) and quinazolin-4(3*H*)-ones (**IIIb-f**) in high yields by the reductive desulfurization of 2-thioxo-4(3*H*)-quinazolinones (**Ia-f**) with nickel boride in dry methanol at ambient temperature following a simple work up procedure. The nickel boride was prepared *in situ* from anhydrous nickel chloride and sodium borohydride in dry methanol. An initial examination was carried out for the reductive desulfurization of 3-phenyl-2-thioxo-4(3*H*)-quinazolinone (**Ia**) as a model substrate, by changing the molar ratios of substrate to nickel chloride to sodium borohydride in various solvents. The reaction of **Ia** with nickel boride using 1:3:9 molar ratio of substrate:$NiCl_2$:$NaBH_4$ in dry methanol was complete in 30 min (run 1) and gave 92% of 3-phenyl-2,3-dihydro-4(1*H*)-quinazolinone (**IIa**), whereas with lower molar ratios of substrate to nickel chloride to sodium borohydride, the reaction was incomplete and resulted in a mixture of products. Reactions of **Ia**, when carried out with nickel boride in dry dichloromethane, tetrahydrofuran and dioxane using different molar ratios of substrate to nickel boride, proceeded very slowly and were incomplete even after 24 h. Though the reaction of **Ia** with nickel boride (molar ratio 1:3:9) in dry dimethylformamide was complete in 30 min, removal of traces of DMF from the reaction mixture posed some difficulties unlike the reaction in dry methanol (run 1). Thus dry methanol was considered as the solvent of choice and was employed in all further reactions. The reaction of **Ia** when carried out with hydrated nickel chloride and ordinary methanol using 1:3:9 molar ratio gave lower yield (80%) of **IIa** and also required longer reaction time (90 min) for completion. There was very little reaction of **Ia** with sodium borohydride alone even after 24 h unlike the quantitative desulfurization with nickel boride in 30 min. Also the starting material **Ia** was recovered unchanged when treated with nickel chloride only. The desulfurization is thus undoubtedly proceeding due to the involvement of nickel boride formed *in situ.*

The scope of the reagent was then extended to other functionalized 3-aryl-2-thioxo-4(3*H*)-qinazolinones (**Ib-g**) (Scheme 1). Since nickel boride is reported to behave differently under different conditions [7,8], it was decided to investigate if reaction conditions could be further modified so as to bring about desulfurization with partial reduction to afford 3-aryl-4(3*H*)-quinazolinones (**III**). All the results are listed in Table 1. It is obvious from Table 1

Scheme 1



Ia-f **IIa-g** **IIIa-f**

a: R = H, Ar = C_6H_5
b: R = H, Ar = 4-MeC_6H_4
c: R = H, Ar = 4-$OMeC_6H_4$
d: R = H, Ar = 4-BrC_6H_4
e: R = H, Ar = 4-ClC_6H_4
f: R = Ar = H
g: R = CH_3, Ar = C_6H_5

Table 1

Reactions of 3-Aryl-2-thioxo-4(3*H*)-quinazolinones with Nickel Boride in dry MeOH [a] at Ambient Temperature

Run No.	Substrate(s) **I**	Molar ratio S:$NiCl_2$:$NaBH_4$	Time (h)	Products **II**	Products **III**	% isolated yields [b]
1.	**Ia**	1:3:9	0.5	**IIa**	–	92 [6a]
2.	**Ib**	1:7:21	6.5 [c]	**IIb**	–	88 [9]
3.	**Ib**	1:10:10	0.5	–	**IIIb**	85 [10]
4.	**Ic**	1:4:12	0.5	**IIc**	–	79 [6a]
5.	**Ic**	1:3:9	0.5	–	**IIIc**	84 [6a]
6.	**Id**	1:5:5	24	–	–	– [d]
7.	**Id**	1:10:10	3.5	**IIa** [e]	–	87 [6a]
8.	**Id**	1:4:12	0.25	–	**IIId**	82 [6a]
9.	**Ie**	1:4:12	.25	**IIe**	–	82 [9]
10.	**Ie**	1:10:10	0.5	–	**IIIe**	85 [11]
11.	**If**	1:5:15	2.5 [f]	**IIf**	–	86 [12]
12.	**If**	1:3:9	4.5	–	**IIIf**	85 [13]
13.	**Ig**	1:3:9	24	**IIg**	–	69 [g]
14.	**Ig**	1:5:15	2.5	**IIg**	–	90 [14]

[a] 25 mL of dry MeOH was used/g of the substrate; [b] Isolated yields of recrystallised products; [c] Reaction was complete after 15 min, however reaction was continued till TLC of the reaction mixture showed the presence of a single product; [d] Reaction was incomplete even after 24 h but showed the formation of two products with overlapping R_f values; [e] The corresponding debrominated product IIa was isolated; [f] Reaction was complete after 1.5 h, however reaction was continued till TLC showed the formation of single product; [g] Starting material (29%) was also recovered.

that 3-aryl-2-thioxo-4(3*H*)-quinazolinones (**Ib-g**) can be reductively desulfurized with nickel boride in dry methanol at ambient temperature to afford 2,3-dihydro-4(1*H*)-quinazolinones (**IIa-g**) or 3-aryl-4(3*H*)-quinazolinones (**IIIa-f**) in quantitative yields by changing the stoichiometric of substrate to nickel chloride to sodium borohydride. The reagent shows high selectivity towards desulfurization and does not affect the amide carbonyl group. The reaction of 4-bromophenyl-2-thioxo-4(3*H*)-quinazolinone (**Id**) with nickel boride in 1:10:10 molar ratio of substrate:$NiCl_2$:$NaBH_4$ resulted in the concomitant debromination to afford 3-phenyl-2,3-dihydro-4(1*H*)-quinazolinone as the sole product (run 7). However, no such debromination was observed when reaction was carried out in the molar ratio 1:4:12, which exclusively led to the formation of 3-(4-bromophenyl)-4(3*H*)-quinazolinone (run 8). Furthermore, no dechlorinated product was isolated in the reaction of **Ie** with nickel boride in either of the above molar ratios (runs 9-10).

The formation of 2,3-dihydro-4(1*H*)-quinazolinones (**IIa-f**) is proposed to be proceeding by the reduction of quinazoline-4(3*H*)-ones (**IIIa-f**), formed initially, by the reductive desulfurization of **Ia-f**. This observation has been confirmed by an independent reaction of 3-(4-tolyl)-4(3*H*)-quinazolinone (**IIIb**) with nickel boride in 1:2:6 molar ratio (substrate:$NiCl_2$:$NaBH_4$) in dry methanol at ambient temperature. The reaction was complete in 30 min and the product isolated after work up was found to be 3-(4-tolyl)-2,3-dihydro-4(1*H*)-quinazolinone (**IIb**). However, the formation of the product **III** by independent pathways cannot be ruled out. No colloidal sulfur was formed in any of these reactions. The desulfurization is believed to be proceeding by hydrogenolysis of the CH-SH bond obtained from reduction of C=S bond. It is further observed that nickel boride loses its activity with time, since no desulfurization was observed in the reaction of **Ia** with preformed nickel boride after 72 h.

We conclude that nickel boride is a simple and convenient reagent for the reductive desulfurization of 2-thioxo-4(3*H*)-quinazolinones. The procedure offers several advantages like mild reaction conditions, greater selectivity, cleaner reaction products, operational simplicity and ease of isolation of products which makes it a useful process for the synthesis of novel quinazolinone derivatives. Further synthetic applications of this reagent are under investigation in our laboratory.

EXPERIMENTAL

Compounds **Ia, Ie** and **Ig** were prepared by the condensation of 2-aminobenzoic acids with aryl isothiocyanates [15] and compounds **Ib-d** were prepared by the condensation of 2-aminobenzoic acids with respective monosubstituted arylthioureas [16]. Compound **If** was prepared by following the described procedure involving condensation of isatoic anhydride with thiourea [17]. Sodium borohyride (E. Merck) and nickel chloride (S.D. Fine) were used in all the reactions.

In a typical procedure, 2-thioxo-4(3H)-quinazolinone (**I**) (1g, n mmol), anhydrous nickel chloride (see Table 1) and dry methanol (25 mL) were placed in a 100 mL conical flask fitted with a condenser and a mercury trap. The flask was mounted over a magnetic stirrer. Sodium borohydride (*see* Table 1) was added very cautiously while stirring the solution vigorously at room

temperature. After complete disappearance of the starting material as monitored by TLC (eluent – benzene:ethyl acetate::90:10;v/v), the reaction mixture was filtered on pump through a celite pad (~ 1 inch). Nickel boride precipitate was washed with methanol (2 x 10 mL). The combined filtrate was diluted with water (~ 50 mL) and extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate extract was dried over anhyd. $MgSO_4$, filtered and concentrated under reduced pressure on a Büchi rotavapor to afford **II** or **III** as indicated in Table 1. Analytically pure samples were obtained by crystallization from ethanol or purified by column chromatography (run 13) over silica gel (100-200) mesh using benzene:ethyl acetate as eluent. The products were analysed by mp, IR, NMR and mass spectra; **IIb**: ^{1}H NMR (60MHz, $CDCl_3$): δ 8.05 (s, 1H), 6.70-7.50 (m, 8H), 5.0 (s, 2H), 2.40 (s, 3H); MS found : m/z: 238 ($M^{+\cdot}$ 35 %); **IIIb**: ^{1}H NMR (60MHz, $CDCl_3$): δ 7.0-8.5 (m, 9H), 2.45 (s, 3H); MS found : m/z: 236 ($M^{+\cdot}$ 20 %).

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