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On the reaction of anthranilic acid with thionyl chloride : Iminoketene intermediate formation

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2-(Sulfinylamino) benzoyl chloride is formed on treating anthranilic acid with thionyl chloride. The formation of iminoketene intermediate from 2-(sulfinylamino) benzoyl chloride is established and the reactions carried out using the intermediate are described.

Keywords: Iminoketene intermediate, anthranilic acid, thionyl chloride, schiff bases, dihydroquinazolin-4 (1*H*)-ones, dibenzo [*b,f*] [1,5] diazocine-6,12-(5*H*,11*H*)-dione, 2-(sulfinylamino) benzoyl chloride, alkyl anthranilates

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It has been reported that sulfinamide anhydride[1] is formed when anthranilic acid is treated with thionyl chloride under anhydrous conditions. Garin *et al.*[2] reported that no sulfinamide anhydride was formed in the reaction of anthranilic acid with thionyl chloride. They reported that 2-(sulfinylamino) benzoyl chloride was formed, in accordance with an earlier observation[3], under the same reaction conditions. Our interest in the addition reactions of 2-(sulfinylamino) benzoyl chloride and the physiological activities[4] of its products prompted us to re-examine the reaction between anthranilic acid and thionyl chloride.

The present paper not only confirms the formation of 2-(sulfinylamino) benzoyl chloride in the reaction of anthranilic acid **1** with thionyl chloride but also suggests the formation of iminoketene **7** under the reaction conditions.

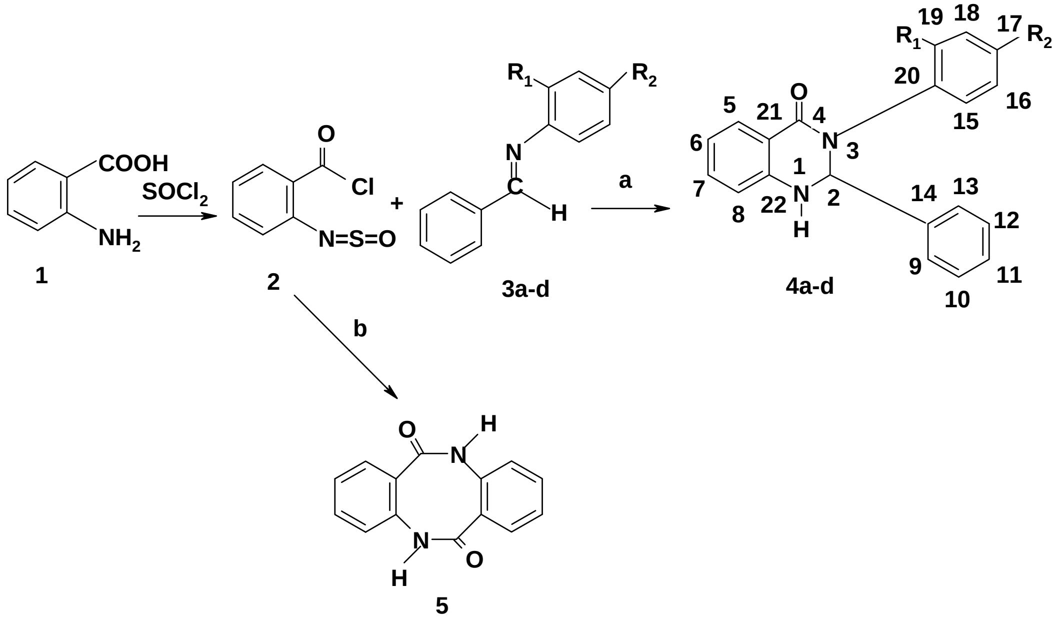
2-(Sulfinylamino) benzoyl chloride **2** on treatment with azomethines **3a-d** in dry benzene solution afforded dihydroquinazolin-4 (1*H*)-ones **4a-d** in good yield along with a small amount of dibenzo [*b,f*] [1,5] diazocine-6,12-(5*H*,11*H*)-dione **5** (**Scheme I**, **Table I**). Dibenzo [*b,f*] [1,5] diazocine-6,12-(5*H*,11*H*)-dione **5** was also isolated, on keeping **2** for 24 hr[5].

The formation of **4a-d** and **5** was envisaged through the formation of an iminoketene intermediate.

The course of the reaction was monitored by GCMS and IR spectrometers. The reaction of anthranilic acid and thionyl chloride was carried out under dry nitrogen and the reaction product was distilled under reduced pressure to remove excess thionyl chloride and HCl. An immediate GCMS analysis under dry conditions of the reaction mixture indicated the presence of 2-(sulfinylamino) benzoyl chloride (m/z = 201). No peak was observed at m/z = 183, indicating the absence of sulfinamide anhydride as proposed by Kametani *et al.*[1]. Besides the absence of peak at m/z = 119 also indicated the absence of formation of iminoketene under the dry conditions. However when the reaction mixture was exposed to atmosphere for 35 minutes, peak at m/z 119 (45%) and also at m/z 64 (100%), 36 (25%) and 38 (8.2%) were developed plausibly due to the formation of iminoketene, sulphur dioxide, HCl^{35} and HCl^{37} respectively.

The IR spectrum of the reaction mixture after 35 minutes developed a ν_{max} 2130 cm^{-1} indicating a ketene functionality. Besides, we observed the formation of alkyl anthranilates **9b-d** and anthranilic acid **9a** in nearly quantitative yields, when the reaction mixture was treated with alcohols and water respectively (**Scheme II**, **Table II**).

On the basis of these observations the following plausible mechanism for the various reactions (**Scheme II**) is suggested.



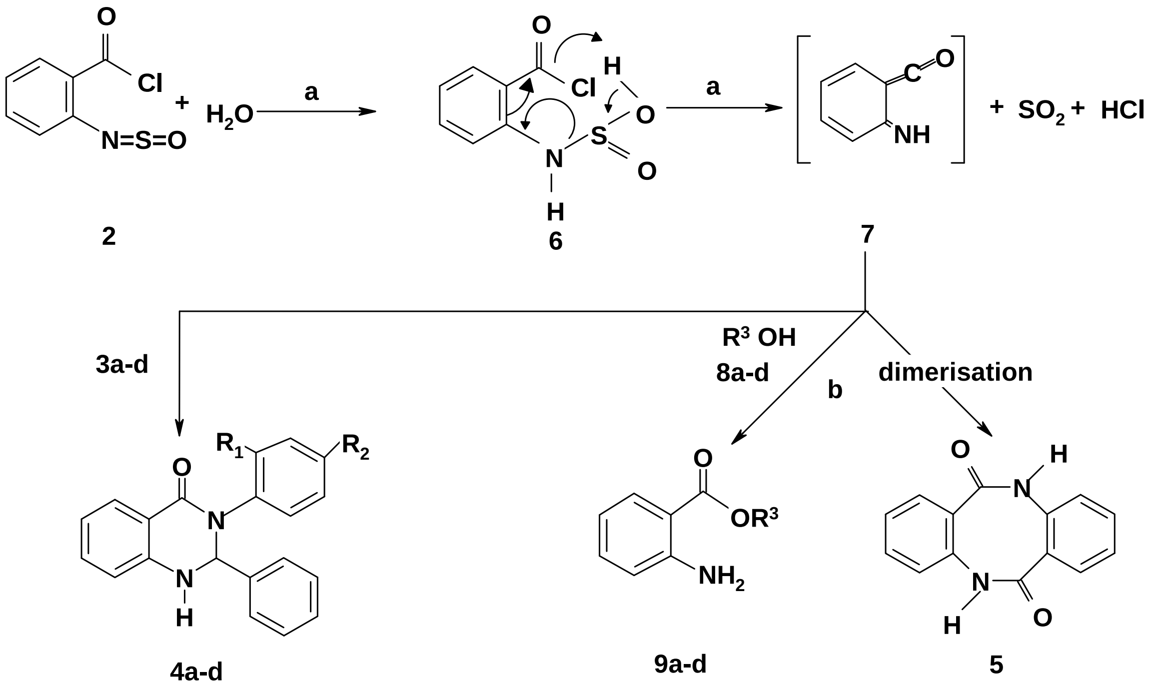
(a) Dry benzene, 2 hr for **4a** and **4b** and 24 hr for **4c** and **4d**, room temp (b) Dry benzene, 24 hr, room temp

Substrate/Product	R_1	R_2
3a/4a	H	H
3b/4b	H	Cl
3c/4c	H	CH_3
3d/4d	OCH_3	H

Scheme I

Table I — Characterization data of compounds **4a-d**

Compd	m.p. °C	Yield (%)	^1H NMR (δ, ppm)	^{13}C NMR (δ, ppm)	MS *m/z* (%)
4a	210	90	7.99 (d, 1H, J=8.2 Hz), 7.97 (t, 1H, J=7.1Hz), 7.33 (d, 1H, J=8.3 Hz), 7.30-7.21 (m, 5H), 7.14-7.01 (m, 5H)), 6.86 (t, 1H, J=7.0 Hz), 6.07 (s, 1H), 4.73 (s, broad, 1H, D_2O exchangeable)	163.0 (C4), 146.5 (C20), 136.2 (C22), 134.3 (C21), 132.8 (C14), 129.4 (C8), 129.2 (C5), 129.0 (C7), 128.9 (C6), 128.7 (C16, C18), 126.8 (C17), 126.2 (C15, C19), 119.4 (C10, C12), 116.9 (C9, C13), 116.7 (C11), 54.3 (C2)	300 (M^+, 18), 223 (50), 209 (15), 208 (100), 77 (20).
4b	221	90	7.99 (d, 1H, J=8.2 Hz), 7.97 (t, 1H, J=7.1 Hz), 7.33 (d, 1H,J=8.3 Hz), 7.25 (d, 2H, J=8.0 Hz), 7.23 (d, 2H, J=8.0 Hz), 7.14-7.01 (m, 5H), 6.87 (t, 1H, J=7.0 Hz), 6.06 (s, 1H), 4.59 (s, broad, 1H, D_2O exchangeable).	164.5 (C4), 133.9 (C20), 130.3 (C22), 129.1 (C21) 129.0 (C14), 128.9 (C17), 128.7 (C8), 128.3 (C5), 128.1 (C7), 127.2 (C6), 126.7 (C16, C18), 119.7 (C15, C19), 114.7 (C10, C12), 113.6 (C9, C13), 113.5 (C11), 54.3 (C2)	334 (M^+, 12), 336 (4), 257 (34), 209 (48), 208 (100), 77 (12).
4c	188	89.8	8.00 (d, 1H, J=8.2 Hz), 7.97 (t, 1H, J=7.1Hz), 7.33 (d, 1H, J=8.3 Hz), 7.27 (d, 2H, J=8.0 Hz), 7.14-7.01 (m, 5H), 6.86 (t, 1H, J=7.0 Hz), 6.61 (d, 2H, J=9.0 Hz), 6.04 (s, 1H), 4.63 (s, broad, 1H, D_2O exchangeable), 2.26 (s, 3H,CH_3).	163.0 (C4), 145.3 (C20), 140.1 (C22), 138.0 (C21), 136.4 (C14), 133.7 (C17), 129.5 (C8), 129.1 (C5), 128.9 (C7), 128.7 (C6), 126.9 (C16, C18), 126.8 (C15, C19), 119.5 (C10, C12), 116.9 (C9, C13), 114.7 (C11), 54.3 (C2), 21.1 (Me at C17)	314 (M^+, 15), 237 (30), 209 (15), 208 (100), 77 (20).
4d	190	70	8.03 (d, 1H, J=8.2 Hz), 8.00 (t, 1H, J=7.2 Hz), 7.93 (d, 1H, J=8.00 Hz), 7.90 (d, 1H, J=8.3 Hz), 7.36 (t, 1H, J=7.20 Hz), 7.30 (t,1H, J=7.2 Hz), 7.25-7.15 (m, 5H,), 7.05 (t,1H, J=7.00 Hz),6.78 (d, 1H, J=8.00 Hz), 6.19 (s, 1H), 3.77 (s, 3H, CH_3), 4.58 (s, broad,1H, D_2O exchangeable).	164.5 (C4), 146.5 (C20), 140.5 (C19), 134.4 (C22), 132.5 (C21), 129.7 (C14), 129.4 (C8), 129.2 (C5), 129.0 (C7), 128.2 (C6), 127.8 (C15), 123.6 (C17), 121.2 (C16), 120.5 (C18), 117.4 (C10, C12), 116.7 (C9, C13),114.5 (C11), 57 (Me of MeO at C19), 55.7 (C2)	330 (M^+, 30), 253 (33.8), 209 (12.5), 208 (100), 77 (15).



(a) 2-(sulfinylamino) benzoyl chloride kept open in contact with atmosphere. (b) In the presence of water and alcohols

Substrate / Product	R^3
8a / 9a	H
8b / 9b	CH_3
8c / 9c	*n*-butyl
8d / 9d	*iso*propyl

Scheme II

Table II — Characterization data of compounds **9b-d**

Compd	m.p. °C	Yield (%)	^{1}H NMR (δ, ppm)	MS *m/z* (%)
9b	Liquid	99.5	7.79 (d, 1H, *J*=7.9 Hz), 7.15 (t, 1H, *J*=8.0Hz), 6.82 (t, 1H, *J*=7.9Hz), 6.55 (d, 1H, *J*=7.9Hz), 5.43 (s, 2H, broad, exchangeable with D_2O), 3.74 (s, 3H).	151 (M^+ 10.43), 120 (6), 119 (100), 92 (84.36).
9c	Liqu#id	99.4	8.27 (d, 1H, *J*=6.8 Hz), 7.77 (d, 1H, *J*=6.8 Hz), 7.47 (t, 1H, *J*=7.2Hz), 7.44 (t, 1H, *J*=7.5Hz), 5.29 (s, 2H,broad, exchangable with D_2O), 4.31 (t, 2H, *J*=6.5Hz), 1.6 -1.4 (m, 2H), 1.3-1.1 (m, 2H), 1.00 (t, 3H, *J*=6.2Hz,).	193 (M^+ 100), 137 (1.5), 120 (11), 119(24), 92 (42.59).
9d	liquEid	99.3	8.24 (d, 1H, *J*=6.7 Hz), 7.77 (d, 1H, *J*=6.7 Hz), 7.54 (t, 1H, *J*=7.0 Hz), 7.46 (t, 1H, *J*=6.9Hz,), 5.30 (s, 2H), 4.15 - 3.90 (m, 1H), 1.1 (d, 6H,, *J*=6.9 Hz).	179 (M^+ 42), 137 (17), 120 (66), 119 (33), 92 (100).

Experimental Section

NMR spectra were recorded in Bruker 300 MHz FT-NMR spectrometer using samples dissolved in $CDCl_3$ and chemical shifts are reported in δ (ppm) relative to Me_4Si (^{1}H NMR) or $CDCl_3$ (^{13}C NMR) as internal standards. IR spectra, were recorded in Bomem MB Series FT-IR spectrophotometer. IR spectra of alkyl anthranilates and changes occurring to 2-(sulfinylamino) benzoyl chloride were monitored using Thermo Nicolet Avtar 370 DTGS FT-IR spectrophotometer. Electron impact mass spectra were obtained using Varian 1200L MS spectrometer. CHN analyses were recorded on an Elementar Vario EL III CHN analyzer. Melting points were recorded on Mel-temp II Laboratory Devices, USA and are uncorrected. All reactions were monitored by thin layer chromatography

(TLC); visualization was effected with a UV lamp. Azomethines were prepared according to literature procedure, purified by column chromatography and recrystallised from methanol before application. The solvents and other chemicals used for the reactions were purified and/or dried as per the standard literature methods. Thionyl chloride was purchased from Qualigens FINE CHEMICALS and used as such.

General procedure for the preparation of dihydroquinazolin-4(1*H*)-ones. To 2-(sulfinylamino) benzoyl chloride **2** (2.73 mmole) were added different Schiff bases **3a-d** (2.73 mmole) in dry benzene (20 mL) and kept for 2 hr in the case of **3a** and **3b** and 24 hr in the case of **3c** and **3d**. Excess solvent was distilled off in vacuum and the residue was dissolved in $CHCl_3$ (20 mL). The organic layer was washed successively with 10% $NaHCO_3$ (5 × 10 mL), water (7 × 10 mL) and finally dried over anhydrous $MgSO_4$. The residue obtained was chromatographed over silica gel using CH_2Cl_2 as eluant in the case of **4a** and **4b**, CH_2Cl_2 - CH_3OH (9 : 1) in the case of **4c** and $CHCl_3$ - $CH_3COOC_2H_5$ (85 : 15) in the case of **4d**.

2,3-Diphenyl-2,3-dihydroquinazolin-4(1*H*)-one 4a. It was obtained as cream coloured crystalline platelets (90%). IR (KBr, cm^{-1}): 3299 (NH stretch), 1640 (C=O stretch); Anal. Calcd for $C_{20}H_{16}N_2O$: C, 80.00; H, 5.33; N, 9.33; O, 5.33. Found: C, 80.02; H, 5.32; N, 9.35; O, 5.31%.

3-(4-Chlorophenyl)-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one 4b. It was obtained as a cream coloured solid (90%). IR(KBr, cm^{-1}): 3305.51 (NH stretch),1638.79 (C=O stretch); Anal. Calcd for $C_{20}H_{15}ClN_2O$: C, 71.85; H, 4.49; Cl, 10.48; N, 8.38; O,4.79. Found: C, 71.87; H, 4.48; Cl, 10.48; N, 8.39; O, 4.78%.

3-(4-Methylphenyl)-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one 4c. It was obtained as a pale yellow solid (89.80%). IR(KBr, cm^{-1}): 3305.75 (NH stretch), 1638.79 (C=O stretch); Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.25; H, 5.73; N, 8.92; O,5.10. Found: C, 80.27; H, 5.74; N, 8.90; O, 5.09%.

3-(2-Methoxyphenyl)-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one 4d. It was obtained as a lemon yellow solid (70.0%). IR (KBr, cm^{-1}): 3293 (NHstretch), 1635 (C=Ostretch); Anal. Calcd for $C_{21}H_{18}N_2O_2$: C,76.37; H,5.45; N,8.48; O,9.7. Found: C, 76.38; H, 5.44; N, 8.50; O, 9.68%.

Small amount of the dimer, dibenzo [*b,f*] [1,5] diazocine-6,12-(5*H*,11*H*)-dione **5** (detected by TLC) was also obtained when 50% petroleum ether + 50% benzene was used as eluant in all the above cases.

Dibenzo [*b,f*] [1,5] diazocine-6,12-(5*H*,11*H*)-dione 5. 2-(Sulfinylamino) benzoyl chloride **2** (3.31 mmole) in dry benzene (20 mL) was kept overnight. Excess solvent was distilled off in vacuum and the residue was dissolved in $CHCl_3$ (20 mL), which was washed with 10% $NaHCO_3$ (3 × 10 mL), water (3 × 10 mL), dried over anhydrous $MgSO_4$ and chromatographed over silica gel using petroleum ether - benzene (1: 1) as eluant to afford pure dibenzo [*b,f*] [1,5] diazocine-6,12-(5*H*,11*H*)-dione **5**, as a lemon yellow solid (350 mg, 88.55%), m.p. 166°C.

Alkyl anthranilates 9b-d. A mixture of 2-(sulfinylamino) benzoyl chloride **2** (441.24 mg, 2.19 mmole) and respective aliphatic alcohols (2.19 mmole), was shaken well for 1 hr. The mixture was chromatographed over basic alumina (70-230 mesh). Pure alkyl anthranilate was eluted out with petroleum ether and removal of solvent gave pure liquid samples of methyl, *n*-butyl and *iso*propyl anthranilates respectively.

9b. IR (KBr, cm^{-1}) 3480.95, 3370.79 (NH_2), 1689.56 (C=O); Anal. Calcd. For $C_8H_9NO_2$: C, 63.58; H, 5.96; N, 9.25; O, 21.21. Found C, 63.57; H, 5.97; N, 9.24; O, 21.22%.

9c. IR (KBr, cm^{-1}) 3068.75, 3041.74 (NH_2), 1685.79 (C=O); Anal. Calcd. For $C_{11}H_{15}NO_2$: C, 68.39; H, 7.77; N, 7.25; O, 16.59. Found: C, 68.40; H, 7.76; N, 7.26; O, 16.58%.

9d. IR (KBr, cm^{-1}) 3068.5, 3041.74 (NH_2), 1687.71 (C=O); Anal. Calcd. For $C_{10}H_{13}NO_2$: C, 67.04; H, 7.26; N, 7.82; O, 17.88. Found: C, 67.05; H, 7.25; N, 7.81; O, 17.89%.

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