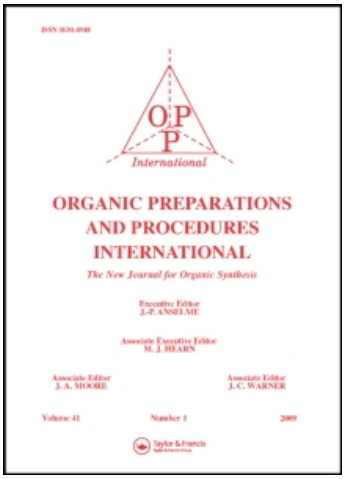

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

VILSMEIER REACTION OF 3-METHYL-N-(4'-SUBSTITUTED)-AZOBENZENESULFONAMIDO)-2-QUINOXALINONE DYES

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To cite this Article Awad, I. M. A.(1993) 'VILSMEIER REACTION OF 3-METHYL-N-(4'-SUBSTITUTED)-AZOBENZENESULFONAMIDO)-2-QUINOXALINONE DYES', Organic Preparations and Procedures International, 25: 3, 347 — 352
To link to this Article: DOI: 10.1080/00304949309457975
URL: http://dx.doi.org/10.1080/00304949309457975

VILSMEIER REACTION OF 3-METHYL-N-(4'-SUBSTITUTED)-AZOBENZENESULFONAMIDO)-2-QUINOXALINONE DYES†

Submitted by (09/02/92)

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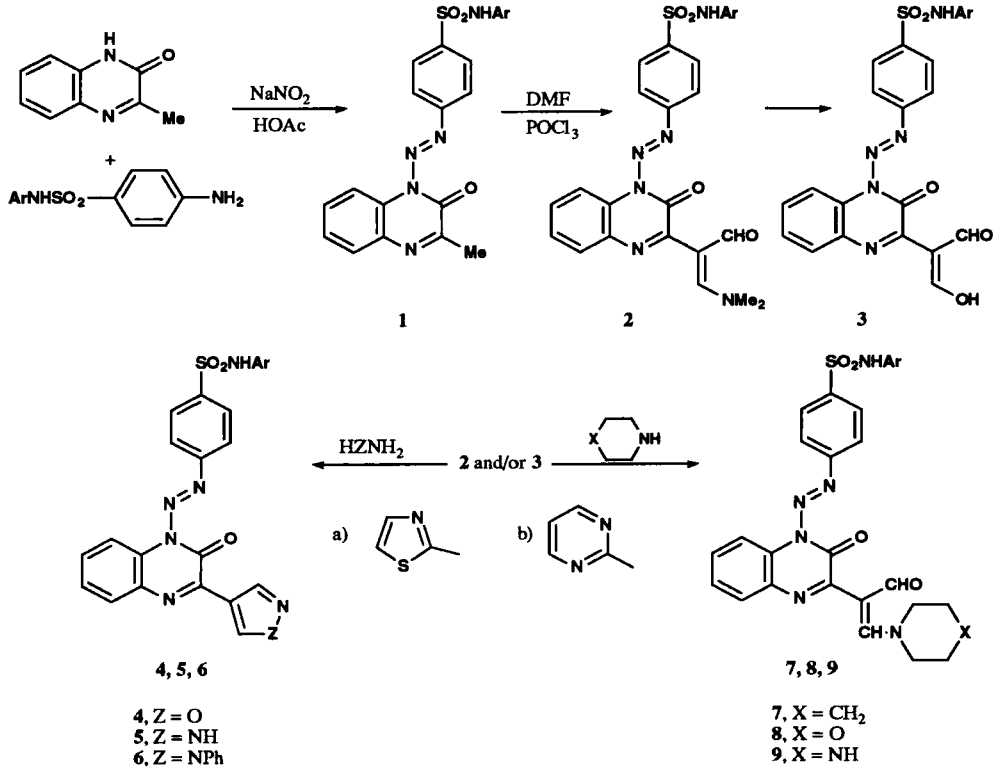
A literature survey has revealed that the chemistry of quinolines bearing sulfonamide groups has attracted special attention due to their therapeutic activity.[1] It seemed of interest to combine sulfonamide derivatives with 3-methyl-2-quinoxalinone to synthesize some new azobenzenesulfonamido-2-quinoxalinone dyes[2] with different heterocyclic moieties at the 3-position of the 2-quinoxalinone moiety with Vilsmeier reagent[3] in the hope of improving the pharmacological properties.

The title azo dyes N-azo(*p*-substituted azobenzenesulfonamido)-3-methyl-2-quinoxalinones were synthesized by diazotization of *p*-aminobenzenesulfonamide derivatives followed by coupling with 3-methyl-N-(1H)-2-quinoxalinone in acid medium to give the corresponding azo dyes as 3-methyl-N-(4'-substituted azobenzenesulfonamido)-2-quinoxalinones (**1**) according to the following scheme.



The Vilsmeier reaction[3] to give 3-methyl-N-(4'-substituted azobenzenesulfonamido)-2-quinoxalinones dyes (**1**) was performed under the usual conditions to give the expected dimethylaminoacrolein derivatives (**2**) in good yields after treatment of the reaction mixture with 2% sodium bicarbonate solution. All the compounds synthesized were identified by conventional methods (IR, ^{1}H NMR and elemental analysis).

The aminoacroleins (**2**) and malondialdehyde derivatives (**3**) reacted with hydroxylamine, hydrazine hydrate and phenylhydrazine to give the corresponding new azo dyes containing substituted heterocyclic derivatives (**4, 5** and **6**).

On the other hand, condensation of **2** and **3** with secondary heterocyclic amines afforded the expected aminomethylenes **7, 8** and **9**.

EXPERIMENTAL SECTION

Mps were determined on Kofler melting point apparatus and are uncorrected. Elemental analysis was performed on a Perkin-Elmer 240° Microanalyzer. IR spectra were recorded on a Pye-Unicam SP-200G infrared spectrophotometer (KBr Pellets). 1H NMR spectra were recorded on a Varian EM-390 MHz instrument in a suitable deuterated solvent, using TMS as internal reference.

4'-Substituted Benzenesulfamoyldiazonium Acetates.- These compounds were prepared by diazotization of 4-aminobenzenesulfonamido-2-thiazole and/or 4-aminobenzenesulfonamido-2-diazine (2.45 g, 0.0l mol), dissolved in acetone and 10 mL of 50% acetic acid, with sodium nitrite (0.7 g, 0.01 mol) at 0-5°. The diazonium acetates were used immediately, without separation, for the synthesis of the corresponding azo dyes: (3-Methyl-N-[4'-substituted azobenzenesulfonamido]-2-quinoxalinone dyes.

3-Methyl-N-(4'-substituted)azobenzenesulfonamido)-2-quinoxalinone Dyes (1a,b). General Procedure.- To an ice cold solution of 3-methyl-N-(1H)-quinoxaline-2-one (1.65 g, 0.01 mole) in 25 mL of 10% sodium hydroxide solution, a cold acetic acid solution of the diazonium salt was added dropwise with stirring, the reaction mixture was further stirred for 2 hrs at 5-10°, when a reddish yellow precipitate separated in acidic medium, an excess of cold water was added, the products were collected; washed well with water and crystallized from aqueous ethanol.

3-Methyl-N-(4'-(thiazol-2"-yl)azobenzenesulfonamido)-2-quinoxalinone (1a), mp. 260°, 3.6 g (85%).

IR (KBr): 1725 (CO), 1600 (C=N), 1520 (N=N), 1340 (SO_2 asym.). 1160 (SO_2 sym.), 1370 (SO_2NH) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 2.20 (s, 3H, CH_3), 8.20 (S, 1H ,SO_2NH) 8.25-7.15 (m, 10 aromatic protons).

Anal. Calcd. for $C_{18}H_{14}N_6O_3S_2$: C, 50.69; H, 3.31; N, 19.71; S, 15.04

Found: C, 50.72; H, 3.33; N, 19.68; S, 15.01.

3-Methyl-N-(4'-(diazin-2"-yl)azobenzenesulfonamido)-2-quinoxalinone (1b), mp. 220°, 3.85 g (87%).

IR (KBr): 1720 (CO), 1525 (N=N), 1335 (SO_2 asym.), 1158 (SO_2 sym.), 2365 (SO_2 NH) cm^{-1}.

^{1}H NMR ($CDCl_3$): σ 2.15 (s, 3H, CH_3), 8.30 (s, 1H, SO_2NH), 8.20-7.00 (m, 11 aromatic protons).

Anal. Calcd. for $C_{19}H_{15}N_7O_3S$: C, 54.15; H, 3.59; N, 23.27; S, 7.60

Found: C, 54.12; H, 3.61; N, 23.31; S, 7.54

3-(α-Dimethylaminomethylene-α-formylmethyl)-N-(4'-(substituted)azobenzenesulfonamido)-2-quinoxalinone dyes (2a,b). General Procedure.- To dimethylformamide (10 mL) cooled to -5°, $POCl_3$ (0.08 mole) was added dropwise and the solution mixture left to stand for 15 minutes till the solution became reddish yellow. To this, the quinoxalinone azo dye (**1a,b**, 0.04 mole) dissolved in dimethylformamide (15 mL), was added dropwise with stirring. The reaction mixture was left to stand for 20 min while stirring, then heated to 70° for 6-7 hrs. The cooled reaction mixture was poured into ice-cold water and treated with 100 mL sodium bicarbonate solution 5%, to pH 9. The reddish orange solid that separated was filtered, washed thoroughly with cold water and crystallized from aqueous ethanol.

3-(α-Dimethylaminoethylene-α-formylmethyl)-N-(4'-(thiazol-2"-yl)azobenzenesulfonamido)-2-quinoxalinone (2a), mp. 180°, 3.0 g (70%).

IR (KBr): 1620 (CHO acrolein), 1520 (N=N), 1595 (C=N), 1715 (CO) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 3.30 (s, 6H, $N(Me)_2$, 9.20 (s, 1H, CHO), 6.80 (s, 1H, Acrolein-methine=CHN<), 8.35 (s, 1H, SO_2NH), 8.12-7.10 (m, 10H aromatic protons).

Anal. Calcd. for $C_{22}H_{19}N_7O_4S_2$: C, 51.86; H, 3.76; N, 19.24; S, 12.59

Found: C, 51.91; H, 3.72; N, 19.28; S, 12.61

3-(α-Dimethylaminoethylene-α-formylmethyl)-N-(4'-(diazin-2"-yl)azobenzenesulfonamido)-2-quinoxalinone (2b), mp. 195°, 3.0 g (71%).

IR (KBr): 2625 (CHO acrolein), 1525 (N=N), 1595 (C=N) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 3.18 (s, 6H, $-N(Me)_2$, 9.15 (1H, CHO), 8.30 (s, 1H, SO_2NH), 6.75 (s, 1H, Acrolein-methine=CHN<).

Anal. Calcd. for $C_{23}H_{20}N_8O_4S$: C, 54.76; H, 3.99; N, 24.19; S, 6.36

Found: C, 54.72; H, 4.03; N, 24.16; S, 6.39

3-(α-Hydroxymethylene-α-formylmethyl)-N-(4'-substituted)azobenzenesulfonamido)-2-quinoxalinone dyes (3a, b). General Procedure.- The aminoacrolein derivatives (**2a,b**, 1 g) taken in dilute HCl (20 mL) were heated to 60° for (25 min). The mixture was then filtered, cooled and basified. The brownish yellow solid that separated was filtered, washed well with cold water and crystallized from aqueous ethanol.

3-(α-Hydroxymethylene-α-formylmethyl)-N-(4'-(thiazol-2"-yl)azobenzenesulfonamido)-2-quinoxalinone (3a), mp. 277°, 4.0 g (78%).

IR (KBr): 1626 (CH0 acrolein), 3240 (OH), 1375 (SO_2NH), 1715 (C0), 1520 (N=N) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 6.85 (s, 1H, =CHN< acrolein-methine), 4.60 (s, 1H, enolic OH), 8.20-7.15 (m, 10H aromatic protons), 8.30 (s, 1H, SO_2NH).

Anal. Calcd. for $C_{20}H_{14}N_6O_5S_2$: C, 48.20; H, 2.83; N, 16.86; S, 12.87

Found: C, 48.26; H, 2.80; N, 16.90; S, 12.83

3-(α-Hydroxymethylene-α-formylmethyl)-N-(4'-(diazin-2"-yl)azobenzenesulfonamido)-2-quinoxalinone (3b), mp. 294°, 3.8 g (76%).

IR (KBr): 1625 (CHO acrolein), 3240 (OH), 1372 (SO_2NH), 1525 (N=N), 1725 (CO) cm^{-1}.

^1H NMR ($CDCl_3$): δ 9.25 (s, 1H, CHO acrolein), 4.65 (s, 1H, enolic OH), 6.80 (s, 1H, =CHN< acrolein-methine), 8.30 (s, 1H, SO_2NH), 8.15-7.10 (m, 11H aromatic protons).

Anal. Calcd. for $C_{21}H_{15}N_7O_5S$: C, 52.49; H, 3.78; N; 20.41; S, 6.67

Found: C, 52.54; H, 3.74; N, 20.37; S, 6.69

3-(4'-Isoxazolyl,4'-N'(H)pyrazolyl and 4'-N'(Ph)pyrazolyl)-N(4'-substituted)azobenzenesulfonamido)-2-quinoxalinone dyes (4a,b-6a,b). General Procedure.- To a solution of aminoacrolein derivatives (**2a,b**, **3a,b**) in ethanol (25 mL) was added equimolar quantity (0.01 mole) of hydroxylamine hydrochloride, hydrazine hydrate and/or phenylhydrazine, respectively. The reaction mixture was refluxed for 2 hrs, cooled, concentrated and poured onto crushed ice. The precipitate solid was filtered, washed with water several times and crystallized from ethanol.

3-(4'-Isoxazolyl)-N-(4'-thiazol-2"-yl)azobenzenesulfonamido)-2-quinoxalinone (4a), mp. 280°, 3.5 g (68%).

IR (KBr): 1528 (N=N), 1365 (SO_2NH), 1605 (C=N), 1720 (CO) cm^{-1}.

^1H NMR ($CDCl_3$): δ 9.80 (s, 1H, NH), 8.20-6.85 (m, 12H, aromatic protons), 8.30 (s, 1H, SO_2NH).

Anal. Calcd. for $C_{20}H_{13}N_7O_4S_2$: C, 48.48; H, 2.64; N, 19.79; S, 12.94

Found: C, 48.51; H, 2.61; N, 19.81; S, 12.91

3-(4'-N'(H)pyrazolyl)-N-(4'-thiazol-2"-yl)azobenzenesulfonamido)-2-quinoxalinone (5a), mp. 245°, 3.4 g (67%).

IR (KBr): 3275 (NH), 1365 (SO_2NH), 1525 (N=N), 1720 (CO) cm^{-1}.

^1H NMR ($CDCl_3$): δ 8.25-7.00 (m, 12H, aromatic protons), 9.80 (s, 1H, NH), 8.35 (s, 1H, SO_2NH).

Anal. Calcd. for $C_{20}H_{14}N_8O_3S_2$: C, 50.20; H, 2.95; N, 23.42; S. 13. 40

Found: C, 50.24; H, 2.91; N, 23.44; S, 13.37

3-(4'-N'(Ph)pyrazolyl)-H-(4'-thiazol-2"-yl)azobenzenesulfonamido)-2-quinoxalinone] (6a), mp. 238°, 3.5 g (69%).

IR (KBr): 1525 (N=N), 1365 (SO_2NH), 1715 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): δ 8-30-7.00 (m, 17H, aromatic protons).

Anal. Calcd. for $C_{26}H_{18}N_8O_3S_2$: C, 59.76; H, 3.47; N, 21.44; S, 6.14

Found: C, 59.79; H, 3.44; N, 21.41; S, 6.18

Compound 4b, mp. 260°, 3.3 g (66%).

IR (KBr): 1720 (CO), 1370 (SO_2NH), 1520 (N=N) cm^{-1}.

^1H NMR ($CDCl_3$): δ 9.75 (s, 1H, NH), 8.17-6.80 (m, 13H, aromatic protons), 8.30 (s, 1H, SO_2NH).

Anal. Calcd. for $C_{21}H_{14}N_8O_4S$: C, 51.43; H, 2.88; N, 22.85; S, 6.54

Found: C, 51.41; H, 2.90; N, 22.87; S, 6.58

Compound 5b, 240°, 3.2 g (63%).

IR (KBr): 1525 (N=N), 3280 (NH), 1715 (C=O), 1365 (SO_2NH) cm^{-1}.

1 H NMR ($CDCl_3$): δ 8.2 5-6.95 (m, 13H aromatic protons), 9.80 (s, 1H, NH).

Anal. Calcd. for $C_{21}H_{15}N_9O_3S$: C, 53.27; H, 3.19; N, 26.62; S, 6.77

Found: C, 53.29; H, 3.20; N, 26.60; S, 6.73

Compound 6b, mp. 212°, 3.3 g (65%).

IR (KBr): 1720 (C=O), 1530 (N=N), 1370 (SO_2NH) cm^{-1}.

^1H NMR ($CDCl_3$): δ 8.25-6.95 (m, 18H, aromatic protons), 8.25 (s, 1H, SO_2NH).

Anal. Calcd. for $C_{27}H_{19}N_9O_3S$: C, 59.00; H, 3.48; N, 22.93; S, 5.83

Found: C, 58.89; H, 3.52; N, 22.79; S, 5.90

3-(α-Piperidino-, morpholino- and/or piperazinomethylene-α-formylmethyl)-N-(4'-substituted)azobenzenesulfonamido-}-2-quinoxalinone dyes (7a,b-9a,b). General Procedure.- To the aminoacrolein derivatives (**2a,b** or **3a,b**) (0.01 mole) in ethanol (35 mL) was added 0.01 mole the secondary amines (piperidine, morpholine and piperazine). The mixture was gently heated on a water bath for 40 min, the solid that separated after concentration was collected, washed with cold methanol and dry ethyl ether and crystallized from methanol.

3-(α-Piperidinomethylene-α-formylmethyl)-N-(4'-(thiazol-2"-yl)azobenzenesulfonamido)-2-quinoxalinone (7a), mp. 302°, 3.6 g (71%).

IR (KBr): 1625 (CHO acrolein), 1710 (C=O), 1370 (SO_2NH) cm^{-1}.

1H NMR ($CDCl_3$): δ 2.52, 3.33, 3.38 (2t, 4H, 2α CH_2, 2t, 4H, 2β CH_2; t, 2 H, γ CH_2, piperidine ring), 8.28-6.95 (m, 10H, aromatic protons).

Anal. Calcd. for $C_{25}H_{23}N_7O_4S_2$: C, 53.09; H, 4.10; N, 17.33; S, 11.34

Found: C, 53.10; H, 4.08; N, 17.30; S, 11.36

3-(α-Morpholinomethylene-α-formylmethyl)-N-(4'-thiazol-2"-y])azobenzenesulfonamido)-2-quinoxalinone (8a), mp. 290°, 3.7 g (72%).

IR (KBr): 1716 (C=O), 1375 (SO_2NH), 1525 (N=N) cm^{-1}.

^1H NMR ($CDCl_3$): δ 8.28 - 6.95 (m, 10H, aromatic protons), 9.20 (s, 1H, CHO), 6.82 (s, 1H, acrolein-methine), 2.50, 3.30 (2t, 4H, α CH_2; 2t, 4H, 2β CH_2 morpholine ring).

Anal. Calcd. for $C_{24}H_{21}N_7O_5S_2$: C, 54.35; H, 3.99; N, 18.48; S, 12.09

Found: C, 54.33; H, 4.02; N, 18.43; S, 12.10

3-(α-Piperazinomethylene-α-formylmethyl)-N-(4'-(thiazol-2"-yl)azobenzenesulfonamido)-2-quinoxalinone (9a), mp. 322° 3.6 g (70%).

IR (KBr): 3285 (NH), 1625 (CHO acrolein), 1515 (N=N), 1720 (CO)cm^{-1}.

^1H NMR ($CDCl_3$): δ 9.20 (s, 1H, CHO), 9.85 (s, 1H, NH–), 6.85 (s, 1H, =CH-N acrolein-methine), 2.55, 3.35 (2t, 4H, 2α CH_2; 2t, 4H, 2β CH_2 piperazine ring), 8.10-7.00 (m, 10H, aromatic protons).

Anal. Calcd. for $C_{24}H_{22}N_8O_4S_2$: C, 50.88; H, 3.91; N, 19.78; S, 11.32

Found: C, 50.90; H, 3.88; N, 19.79; S, 11.34

3-(α-Piperidinomethylene-α-formylmethyl)-N-(4'-(diazin-2"-yl)azobenzenesulfonamido)-2-quinoxalinone (7b), mp. 225°, 3.30 g (66%).

IR (KBr): 1625 (CHO acrolein), 1520 (N=N), 1715 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 9.15 (s, 1H, CHO), 6.80 (s, 1H, =CH-N< acrolein-methine), 8.15 (s, 1H, SO_2NH), 2.50, 4.40, 3.32 (2t, 4H, 2α CH_2; 2t, 4H, 2β CH_2; t, 2H, γ CH_2 piperidine ring), 8.20-6.90 (m, 11H aromatic protons).

Anal. Calcd. for $C_{26}H_{24}N_8O_4S$: C, 52.69; H, 4.09; N, 18.91; S, 10.82
Found: C, 52.72; H, 4.05; N, 18.84; S, 10.84

Compound 8b, mp. 270°, 3.50 g (69%).

IR (KBr): 1620 (CHO acrolein), 1525 (N=N), 1720 (C=O), 1370 (SO_2NH)cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 9.05 (s, 1H, CHO), 6.70 (s, 1H, =CH-N<), 2.55, 3.30 (2t, 4H, 2α CH_2; 2t, 4H, 2β CH_2 morpholine ring).

Anal. Calcd. for $C_{25}H_{22}N_8O_5S$: C, 54.94; H, 4.06; N, 20.50; S, 5.87
Found: C, 54.90; H, 4.04; N, 20.55; S, 5.89

Compound 9b, mp. 298°, 3.50 g (70%).

IR (KBr): 1715 (C=O), 1515 (N=N), 1335 (SO_2 asym.), 1160 (SO_2 sym.), 1625 (CHO acrolein), 3285 (NH) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 9.10 (s,1H, CHO), 6.75 (s, 1H, =CH-N<), 9.70 (s, 1H, NH), 2.50, 3.30 (2t, 4H, 2α CH_2; 2t, 4H, 2β CH_2 piperazine ring).

Anal. Calcd. for $C_{25}H_{23}N_9O_4S$: C, 54.16; H, 4.18; N, 22.74; S, 5.78
Found: C, 54.19; H, 4.21; N, 22.70; S, 5.76

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