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REACTION OF BENZOYLENEUREA AND ISATOIC ANHYDRIDE WITH THE VILSMEIER REAGENT

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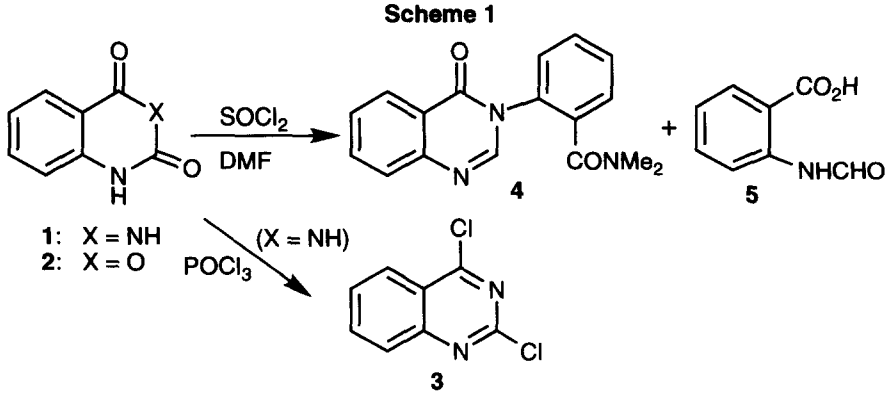
Abstract: A ring opening and dimerization reaction of benzoyleneurea (**1**) or isatoic anhydride (**2**) with thionyl chloride in DMF (Vilsmeier reagent), to yield N,N-dimethyl-2-(4-oxo-3(4H)-quinazolinyl)benzamide (**4**), is described.

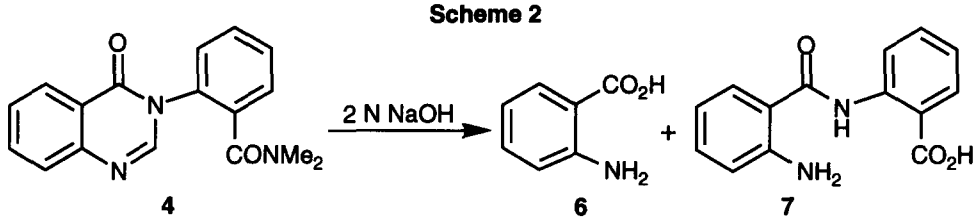
During the course of one of our projects, we required 2,4-dichloroquinazoline (**3**) as a synthetic intermediate. Preparation of (**3**) by a reaction of benzoyleneurea (**1**) with neat phosphorus oxychloride at high temperatures and in the presence of N,N-dimethylaniline is reported in the literature.[1] In an effort to find milder conditions for this purpose we selected Vilsmeier conditions (thionyl chloride and DMF), which have been used for the chlorination at position-6 in nucleoside chemistry.[2] These conditions with benzoyleneurea, however, led to an unexpected product N,N-dimethyl-2-(4-oxo-3(4H)-quinazolinyl)benzamide (**4**). In this paper we wish to report a ring opening and dimerization reaction of benzoyleneurea and isatoic anhydride[3] with the excess of Vilsmeier reagent[4] to yield **4** (Scheme 1).

Scheme 1



Treatment of benzoyleneurea (**1**) with thionyl chloride using DMF as a solvent at 65-70 °C did not yield any of the desired 2,4-dichloroquinazoline (**3**). N,N-dimethyl-2-(4-oxo-3(4H)-quinazolinyl)benzamide (**4**)[5] and N-formylanthranilic acid (**5**) were isolated as major products (Table 1; entry 1). Their structures were assigned based on spectral data. Structure **4** was further confirmed by its hydrolysis with refluxing 2 N NaOH, which yielded anthranilic acid (**6**) and anthraniloylanthranilic acid (**7**)[6] as the expected degradation products (Scheme 2). The identity of **7** was further established by comparison of its spectral data with those of an authentic sample.[6]

Scheme 2



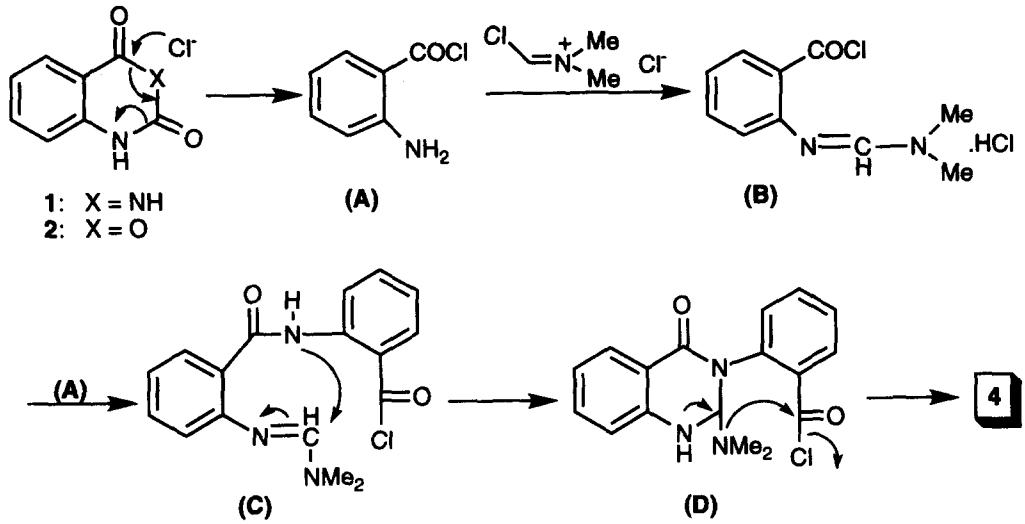
4 **6** **7**

Table 1

Entry	Starting Material	Reagent	Isolated Yield (%)	
			4	**5**
1	Benzoyleneurea (**1**)	$SOCl_2$ / DMF	63	30
2	Benzoyleneurea (**1**)	$POCl_3$ / DMF	55	35
3	Isatoic anhydride (**2**)	$SOCl_2$ / DMF	84	10
4	Anthranilic acid (**6**)	$SOCl_2$ / DMF	62	33
5	2,4-Dichloroquinazoline (**3**)	$SOCl_2$ / DMF	0	0
6	Anthraniloylanthranilic acid (**7**)	$SOCl_2$ / DMF	71	-

A plausible mechanism for the formation of **4** and **5** is illustrated in Scheme 3. An initial ring opening of **1** would yield anthranilic acid chloride (**A**), which would react further with the Vilsmeier reagent to yield intermediate **B**. Reaction of **B** with the acid chloride **A** would lead to the dimeric intermediate **C** which would undergo cyclization followed by migration of the dimethylamino group to yield **4**. Product **5** would emerge from hydrolysis of **B** during work-up. Because ring opening would be more facile in the case of isatoic anhydride (**2**) than **1**, it was treated with the Vilsmeier reagent under identical conditions.[7] This yielded **4** in excellent yields (entry 3). The initial ring opening of benzoyleneurea (**1**) and isatoic anhydride (**2**) with the Vilsmeier reagent to anthranilic acid chloride (**A**) was further evidenced by the fact that anthranilic acid, when subjected to identical conditions, also furnished **4** and **5** (entry 4). Similar reaction of 2,4-dichloroquinazoline (**3**), which had no potential for ring opening to acid chloride (**A**), did not yield any **4** or **5** (entry 5), indicating that initial ring opening is critical for this reaction. Treatment of anthraniloylanthranilic acid (**7**) with the Vilsmeier reagent also yielded **4** in excellent yield (entry 6), suggesting that species **C** is a possible intermediate in the formation of **4**.

Scheme 3



In summary, a ring opening and dimerization reaction of benzoyleneurea or isatoic anhydride with the Vilsmeier reagent, to yield N,N-dimethyl-2-(4-oxo-3(4H)-quinazolinyl)benzamide (**4**), is described.

References and Notes:

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3. Coppola, G. M. *Synthesis* **1980**, 505-536.
4. a) Meth-Cohn, O; Tarnowski, B. *Adv. Heterocyl. Chem.* **1982**, *31*, 207-236. b) Marson, C. M. *Tetrahedron* **1992**, *48*, 3659-3726. c) Meth-Cohn, O. *Heterocycles* **1993**, *35*, 539-557.
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6. Staiger, R. P.; Miller, E. M. *J. Org.Chem.* **1959**, *24*, 1214-1219.
7. Typical procedure: A mixture of starting material (50 mmol) and DMF (40 mL) was heated to 65-70 °C (internal temperature). To the resulting mixture was added $SOCl_2$ (19.7 g, 165 mmol) over a period of 30 min while maintaining an internal temperature of 65-70 °C. The mixture was stirred at the same temperature for 4 h and cooled to 15-20 °C. Water (25 mL) was added dropwise while maintaining an internal temperature of 20-23 °C (bath temperature 5-7 °C) over 25 min. The resulting mixture was basified with 5 N NaOH (100 mL) and extracted with isopropyl acetate (2 X 200 mL).
   The organic layer was separated, washed with brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by silica gel chromatography using ethyl acetate as

the eluant to furnish pure **4**, mp 127-128 °C; ^{1}H NMR ($CDCl_3$, δ) 2.92 (s, 3H), 2.96 (s, 3H), 7.41 (d, 1H, J=8.0 Hz), 7.45 (d, 1H, J=8.0 Hz), 7.55 (m, 3H), 7.78 (m, 2H), 8.12 (s, 1H), 8.29 (d, 1H, J=8.0 Hz); ^{13}C NMR ($CDCl_3$, δ) 34.86, 39.23, 76.69, 77.11, 77.53, 122.13, 126.84, 127.38, 127.62, 127.85, 128.88, 129.3, 130.32, 134.59, 134.84, 135.69, 146.54, 148.06, 160.92, 168.01; MS (m/e) 294 (MH^+); IR (KBr, cm^{-1}) 1683, 1636, 1610.

The aqueous layer was acidified with conc. HCl (15 mL) and extracted with isopropyl acetate (2 X 200 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was triturated with hexane and filtered to give pure **5**, mp 164-165 °C (lit. mp. 165 °C; Hughes, B.; H. Suschitzky, H. *J. Chem. Soc.* **1965**, 875-779).

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