



## Dimerization of Substituted 2-Aminobenzoic Acids under Vilsmeier Conditions : A Novel Route to the Synthesis of 4-(3H)-Quinazolinones.

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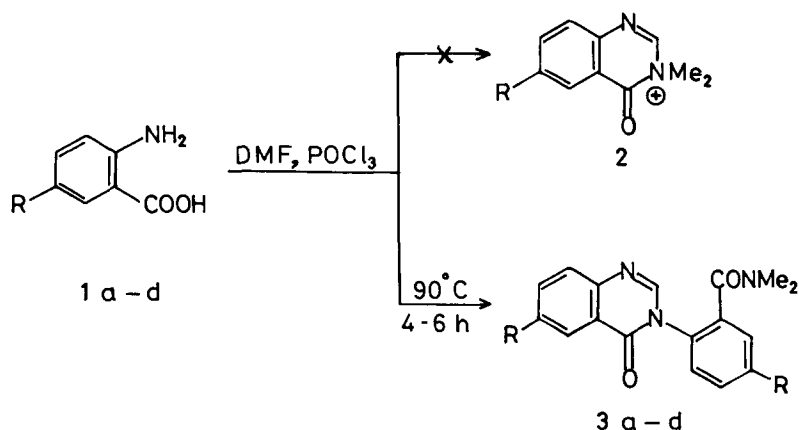
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**Abstract:** Various substituted 2-aminobenzoic acids on treatment with Vilsmeier reagent (DMF/POCl<sub>3</sub>) at 80-90°C undergo a novel dimerization reaction to yield 2-[3,4-dihydro-4-oxo-3-quinazolinoyl]-N,N-dimethyl benzamides. The interruption of dimerization at rt by the addition of primary amines affords the corresponding quinazolinones. Copyright © 1996 Elsevier Science Ltd

4-(3H)-Quinazolinones<sup>1</sup> are reported to exhibit a wide spectrum of biological activities including anthelmintic activity,<sup>2a</sup> analgesic activity,<sup>2b</sup> anti-inflammatory property,<sup>2c</sup> CNS depressant activity,<sup>2d</sup> blood platelet aggregation inhibiting property<sup>2e</sup> etc. The quinazolinones are normally prepared by the treatment of O-acyl anthranils with primary amines at temperatures above 200°C<sup>3a</sup> or by heating O-acyl aminobenzoic acids with the required amine in polyphosphoric acid.<sup>3b</sup> Other methods of synthesis include treatment of phosphoranes with NaH/CH<sub>3</sub>CN,<sup>3c</sup> pyrolysis of Schiff bases derived from 3-amino-1,2,3-triazin-4-one in paraffin oil at 300°C.<sup>3d</sup>

The Vilsmeier-Haack-Arnold reagent is extensively used for formylation<sup>4</sup> of activated aromatic compounds and carbonyl compounds. Vilsmeier reagents also find application in the synthesis of a large number of heterocyclic compounds.<sup>5</sup> Recently some interesting cyclization reactions under Vilsmeier conditions have been reported from this laboratory.<sup>6</sup> In continuation of our interest in this versatile reagent, we have attempted to develop a new strategy towards the synthesis of quinazolinium salts **2** from substituted 2-aminobenzoic acids. But contrary to the expectations 4-(3H)-quinazolinones were directly obtained in a single step in high yields by a novel dimerization reaction (Scheme 1).<sup>7</sup> When an equimolar mixture of two differently substituted anthranilic acids was subjected to Vilsmeier condition, all the four possible dimeric products were obtained in various yields.

Scheme 1

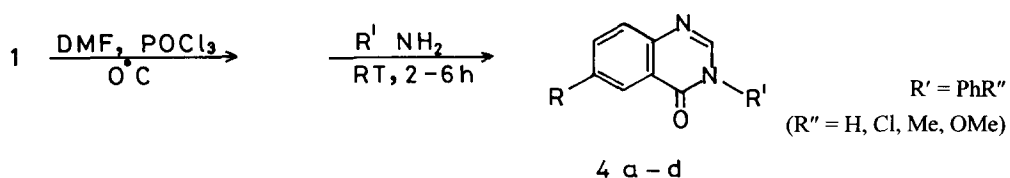


entry	1,3	R	yield of <b>3</b> <sup>a</sup> (%)	Mp ( $^\circ\text{C}$ )
1	<b>a</b>	H	83	126
2	<b>b</b>	Cl	82	181
3	<b>c</b>	Br	86	153
4	<b>d</b>	$\text{CH}_3$	50	135

<sup>a</sup>: All compounds gave satisfactory spectral data and elemental analyses.

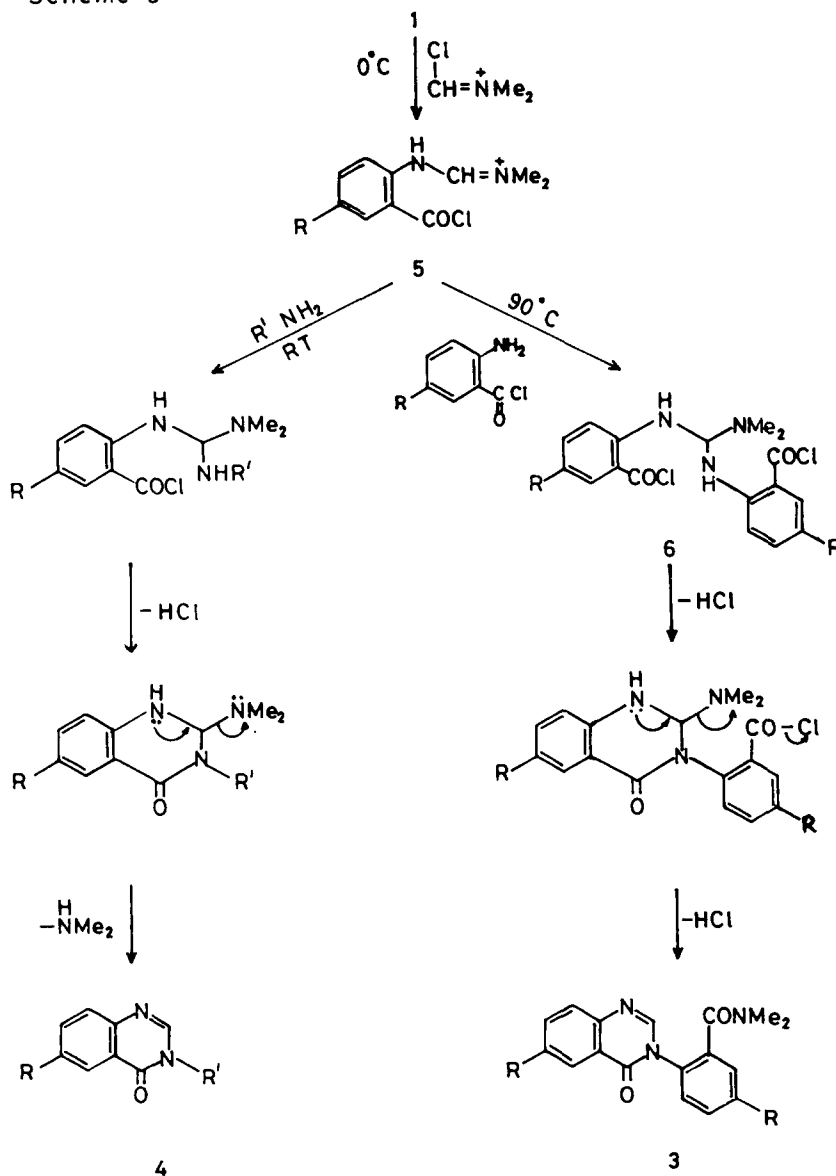
Very few dimerization reactions are reported in the literature under Vilsmeier conditions.<sup>8</sup> Therefore, we pursued the reaction conditions further and observed that even after prolonged intervals of time, no dimeric product could be obtained at temperatures below  $60^\circ\text{C}$ . This prompted us to study the effect of external addition of amines to the reaction mixture at low temperature. When a mixture of 2-aminobenzoic acid and primary amine was treated with Vilsmeier reagent at rt, no major product could be obtained. But when 2-aminobenzoic acid was treated with Vilsmeier reagent at  $0^\circ\text{C}$  followed by the addition of a suitably substituted primary amine at rt, the corresponding quinazolinones were obtained as the only product in low yields (Scheme 2).

Scheme 2



Based on the above findings a plausible mechanism could be proposed for the reaction (Scheme 3). The chloromethyleniminium salt formed from DMF and  $\text{POCl}_3$  reacts with 2-aminobenzoic acid (1) to yield the acid chloride 5 which reacts with another molecule of 1 at high temperature to yield 6. The diacid chloride 6 undergoes spontaneous cyclization followed by migration of dimethylamino group to give 3. When the reaction is interfered at low temperature by the addition of primary amine, the reaction takes the alternate pathway resulting in the formation of 3-substituted quinazolinones 4.

Scheme 3



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## References and Notes

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7. **Typical experimental procedure**  
Preparation of 2-[3,4-dihydro-4-oxo-3-quinazolinoyl]-N,N-dimethyl benzamide (**3a**): 2-aminobenzoic acid (1.37g, 0.01 mole) was dissolved in 5 mL DMF and added dropwise to the Vilsmeier complex prepared from DMF (5 mL) and POCl<sub>3</sub> (2.8 mL). The reaction mixture was stirred at rt and maintained at 90°C for 5h. The resulting mixture was neutralized with crushed ice, extracted with chloroform and purified by passing through a column (6 : 4 petroleum ether : ethyl acetate) to yield **3a** in 83 % yield. mp. 126°C, <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.22 (d, 1H, J=7.9 Hz), 8.05 (s, 1H), 7.72-7.70 (m, 2H), 7.51-7.43 (m, 3H), 7.39-7.32 (m, 2H), 2.89 (s, 3H), 2.85 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 168.01, 160.93, 148.03, 146.53, 135.64, 134.65, 134.58, 130.30, 129.29, 128.86, 127.82, 127.59, 127.37, 126.83; MS (m/e) : 293 (M<sup>+</sup>), Anal. Calcd for C<sub>17</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub> : C, 69.60; H, 5.16; N, 14.33. Found : C, 69.94; H, 5.30; N, 14.63.
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