Pergamon

Tetrahedron Letters, Vol. 37, No. 28, pp. 5015-5018, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01022-2

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

Vattoly J. Majo and Paramasivan T. Perumal *

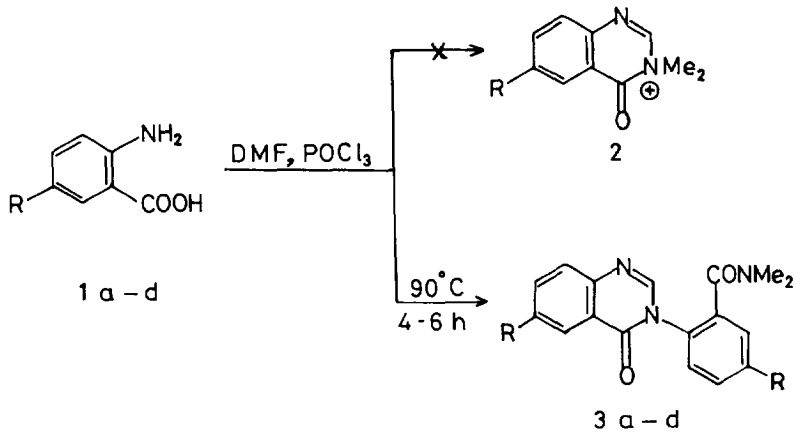
Organic Chemistry Division
Central Leather Research Institute
Adyar, Madras 600 020, India.

Abstract: Various substituted 2-aminobenzoic acids on treatment with Vilsmeier reagent ($DMF/POCl_3$) 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[1] are reported to exhibit a wide spectrum of biological activities including anthelmintic activity,[2a] analgesic activity,[2b] anti-inflammatory property,[2c] CNS depressant activity,[2d] blood platelet aggregation inhibiting property[2e] etc. The quinazolinones are normally prepared by the treatment of O-acyl anthranils with primary amines at temperatures above 200°C [3a] or by heating O-acyl aminobenzoic acids with the required amine in polyphosphoric acid.[3b] Other methods of synthesis include treatment of phosphoranes with NaH/CH_3CN,[3c] pyrolysis of Schiff bases derived from 3-amino-1,2,3-triazin-4-one in paraffin oil at 300°C.[3d]

The Vilsmeier-Haack-Arnold reagent is extensively used for formylation[4] of activated aromatic compounds and carbonyl compounds. Vilsmeier reagents also find application in the synthesis of a large number of heterocyclic compounds.[5] Recently some interesting cyclization reactions under Vilsmeier conditions have been reported from this laboratory.[6] 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).[7] 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

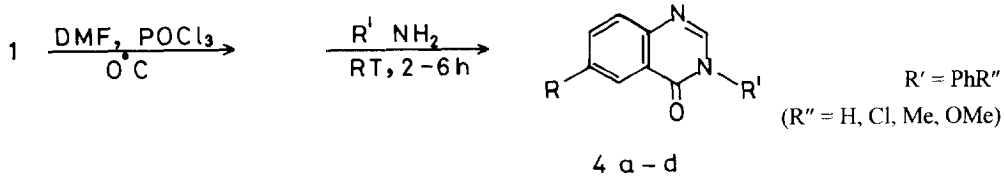


entry	1,3	R	yield of 3[a](%)	Mp (°C)
1	**a**	H	83	126
2	**b**	Cl	82	181
3	**c**	Br	86	153
4	**d**	CH_3	50	135

[a]: All compounds gave satisfactory spectral data and elemental analyses.

Very few dimerization reactions are reported in the literature under Vilsmeier conditions.[8] 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°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°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).

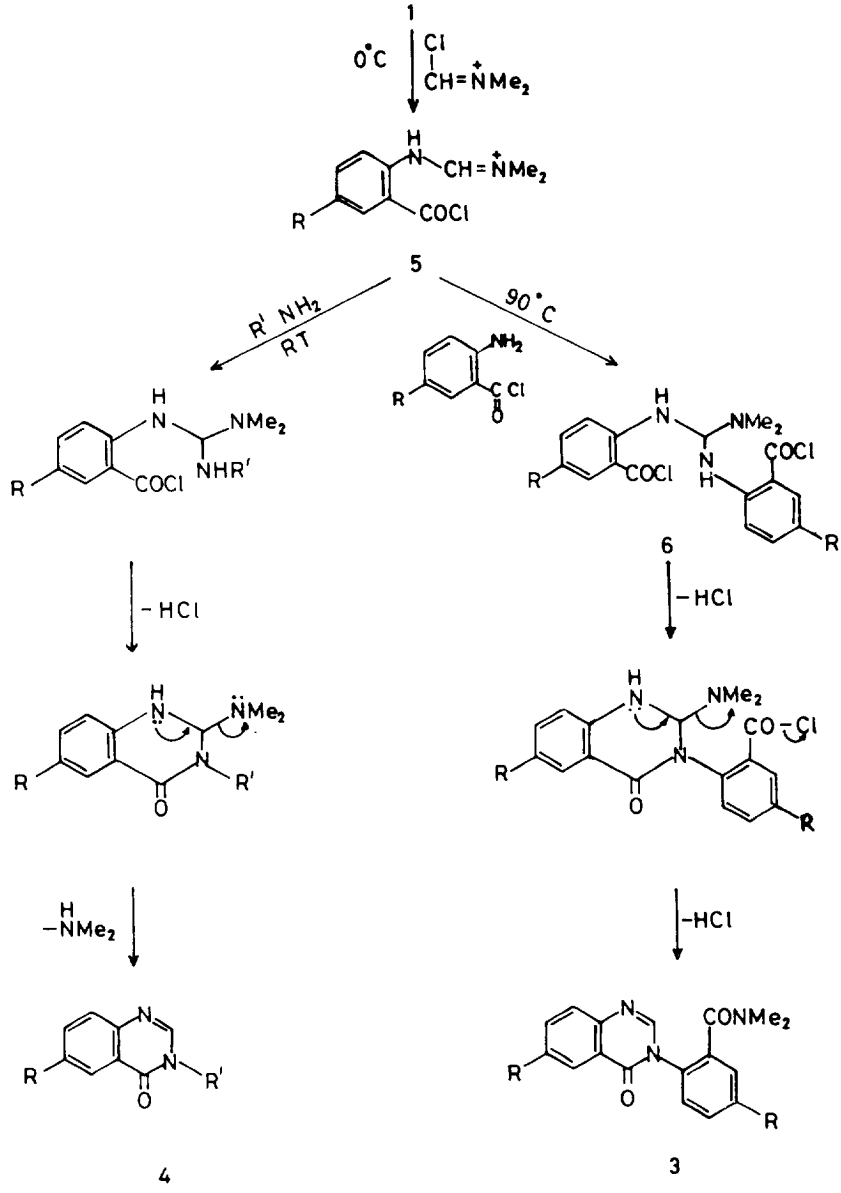
Scheme 2



4 a – d

Based on the above findings a plausible mechanism could be proposed for the reaction (Scheme 3). The chloromethyleniminium salt formed from DMF and $POCl_3$ 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



Acknowledgement. V. J. M. is grateful to CSIR, New Delhi for a fellowship. We are grateful to R.Radhakrishnan for recording mass spectra.

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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 $POCl_3$ (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, ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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^+), Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.60; H, 5.16; N, 14.33. Found : C, 69.94; H, 5.30; N, 14.63.
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(*Received in UK* 10 *April* 1996; *revised* 22 *May* 1996; *accepted* 24 *May* 1996)