Reaction of Solid Acetylanthranil with Methanol Vapor: High Specificity and Enhanced Reactivity

Jacques Vicens*

Laboratoire de Chimie Industrielle, ERA 600, Université Claude Bernard, Lyon, France

L. A. Errede

3M Central Science Laboratories of Central Research, 3M Center, Bldg 201-2s-14, St. Paul, Minnesota 55144

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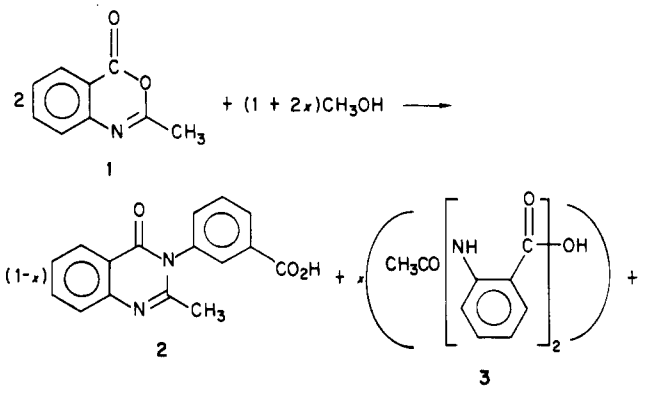
Reactions of organic compounds are more selective when performed in the solid state rather than in solution.[1-4] For example, the elimination in some halides is highly stereospecific when performed in the crystalline state.[5,6] Optical induction has been observed during the reaction of chiral single crystals of chalcone with bromine.[7] The higher reactivity of one enantiomer of a crystalline carboxylic acid with an optically active amine has been noted.[8] Heating thallium(I) salts of β-dicarboxyl compounds with vapors of alkyl iodides results in regiospecific C-alkylation.[9] The reaction of methyl iodide vapors with dispersed solid lithiated sulfinyl carbanion occurs in a complete stereospecificity.[10]

We previously reported that methanolysis of acetylanthranil (1) (i.e., 2-methyl-4*H*-benzoxazin-4-one) in neutral or acidified solution leads to self-condensation products;[11,12] we observed the formation of *N*-(2-carboxyphenyl)-2-methylquinazolin-4-one (2) and/or *o*-(*o*-acetamidobenzamido)benzoic acid (3) along with methyl acetate and dimethyl ether as concomitant side products in accordance with the stoichiometry of eq 1. The value of



x in eq 1 ranged from 1 to 0, depending upon the choice of reaction conditions, (i.e., acidity, temperature, and the presence of water). Presumably these variables alter the equilibria between the intermediates and residual reactants and thus affect the selectivity for product formation via the alternative reaction pathways. We thought that because in solid phase such equilibria may not exist, the reaction in the solid state may be more selective.

Accordingly, we exposed microcrystals of 1 (74 mg; mp 85–86 °C) in a well-closed flask to CH_3OH vapor at 25 °C for 15 h to produce a mixture of liquid and crystals. The mixture was washed with diethyl ether to remove unreacted 1 (6 mg), adsorbed methanol, and methyl acetate. The residue (59 mg, mp 250–252 °C) was identified as 2 by its mixture melting point with an authentic sample (lit.[12] mp 253–254 °C), proton NMR spectrum in $CDCl_3$–Me_2SO-d_6 [δ 2.22 (s, 3 H, CH_3), 7.33–8.52 (m, 8 H, Ar)] MS (70 eV) [*m/e* 280], and by its elemental analysis. Anal. Calcd for $C_{16}H_{11}N_2O_3$: C, 68.81; H, 3.97; N, 10.03. Found: C, 68.5; H, 4.1; N, 10.0.

In another experiment, the liquid portion of the semisolid product mixture was analyzed by gas chromatography (capillary column 80 m long, 0.32 mm i.d., stationary phase Superox 0.1 M, film thickness 0.15 μm), and the molar ratio of $CH_3CO_2CH_3$ to CH_3OH found thereby was 1:9. The molar amount of methyl acetate in the liquid fraction was found to be about equal to the molar amount of 2 isolated in the crystalline fraction. Consistent with the absence of product 3 in the solid fraction, no dimethyl ether was detected in the liquid fraction.

Thus, self-condensation of 1 occurs more easily in the solid state than it does in solution; conversion of 1 in ordered molecular array within the crystals exposed to methanol vapor at 25 °C was 92% complete within 15 h, whereas about 14 days were required to attain this percent conversion in neutral methanol solution.[11] The specificity of this reaction is markedly improved when it is made to occur heterogeneously. Product 2 was produced exclusively when crystals of 1 were exposed to methanol vapor, whereas the ratio of product 2 to product 3 was about 3:1 when the corresponding reaction was made to occur in solution.

Because the selectivity for reaction in the solid state is such that 2 is produced exclusive of 3, the mechanistic pathways suggested earlier[12] for the alternative products can be simplified to that shown in Scheme I. Since water of reaction, produced within the crystals via cyclodehydratation of intermediate 2′ to give 2, is more reactive than the alcohol, intermediate Y reacts preferentially with water to give intermediate Z′ instead of Z. Ultimate conversion of Z′ to 2 occurs as before, but this is now accompagnied by concomitant regerenation of CH_3OH and H_2O instead of CH_3OCH_3 and H_2O. This cyclic chain of events involving Z′ is repeated such that each adjacent 1 is converted in turn to 2 as a function of the rate of methanol permeation, and in accordance with the stoichiometry of eq 2. If product 3 were produced selectively instead of

$$21 + CH_3OH \rightarrow 2 + CH_3CO_2CH_3$$

2, no H_2O would have been generated, and consequently the stoichiometry would have been given eq 3. Presumably, the conversion of 1 to 2 begins at the crystal surface and propagates therefrom until all 1 in the crystal are converted sequentially to product as indeed was the case for the solid state hydrolysis of 1.[13-15] In this conversion

$$21 + 3CH_3OH \rightarrow 3 + CH_3CO_2CH_3 + CH_3OCH_3$$

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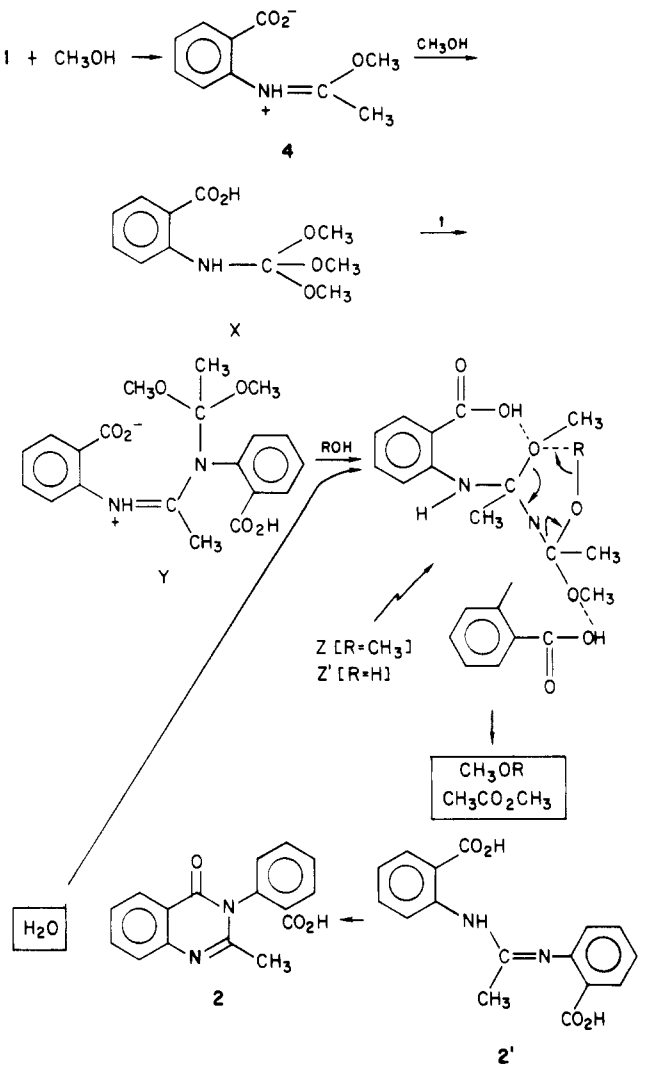
Scheme I[a]



[a] R is CH_3 in the initial cycle, but R is H in all subsequent cycles.

of 1 to *o*-acetamidobenzoic acid by adsorbed water vapor, the reaction was assisted by H-bonding arrays in the crystals, such that nucleophilic attack by adsorbed water molecules occurred exclusively at the C-2 position, i.e., adjacent to the heterocyclic nitrogen atom of 1. It is reasonable to assume, therefore, that similar H-bonding of 1 with $HOCH_3$ may give sequentially intermediates that lead to product 2 perhaps as outlined in Scheme I.

Quite clearly, the high specificity and the enhanced reactivity of the reaction of acetylanthranyl and methanol are directly related to the heterogenous conditions. A similar crystal-orienting influence on rate of reaction was reported by others for the solid-state transformation of methyl *p*-(dimethylamino)benzenesulfonate.[16]

Our future work will be directed toward a better understanding of how enhanced reactivity and improved selectivity is affected by crystal packing. From a more general point of view, such efforts to understand enhancement of chemical reaction rates and improvement of selectivity due to orientation and proximity properties are in relation with mechanisms of enzymatic catalysis.

Registry No. 1, 525-76-8; 2, 4005-06-5; methyl acetate, 79-20-9; methanol, 67-56-1.

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Stable Derivatives of 5,6,7,8-Tetrahydropteridines

William Pendergast* and William R. Hall

Department of Organic Chemistry, Wellcome Research Laboratories, Research Triangle Park, North Carolina 27709

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Folic acid (**1a**) and other 6- and 7-substituted derivatives of pterin (**1b**) undergo chemical or enzymatic reduction in the pyrazine ring to yield the corresponding tetrahydro derivatives **2** (Chart I) which are of central importance in biology and medicine;[1] however, the instability of the hydrogenated derivatives[2] has limited the chemotherapeutic utility of pterins and diaminopteridines to the fully aromatic species.[3] Taylor[4] demonstrated that removal of the electron-donating hydroxy and amino substituents to give the parent pteridine (**3a**) greatly enhanced the stability of the reduced pteridine nucleus (**4a**) compared with that of the reduced pterins **2** and lumazines (**4b**); Clark[5] showed that the presence of the electron-withdrawing group in 4-(ethoxycarbonyl)pteridine (**3b**) greatly increased the stability of the covalently dihydrated species **4d** compared with that of the parent pteridine (**4c**).[6] Thus we predicted that electron-attracting substituents would stabilize 5,6,7,8-tetrahydropteridines even in the presence of those polar, electron-donating groups which are essential for effective binding of pteridines to enzymes.[1] In the present study the synthetic targets were 2-substituted 6,7-dimethyl-5,6,7,8-tetrahydropteridines, a system which is at once simple and of biological relevance because of its relationship to tetrahydro-6,7-dimethylpterin (**2**, $R^1 = R^2 = CH_3$; $R^3 = H$), an experimental substrate for the monooxygenase enzymes which hydroxylate phenylalanine and tryosine.[1a,7]

Discussion and Results

The aromatic pteridines were obtained by condensation of the appropriate 4,5-diaminopyrimidine **5**[8] with diacetyl at the reflux in *tert*-butyl alcohol (Table I). Reductions of the (ethoxycarbonyl)pteridines to the 5,6,7,8-tetrahydro derivatives were carried out with sodium borohydride in methanol at room temperature (Table II).

The latter reactions were followed by thin-layer chromatography in 5% $MeOH/CH_2Cl_2$ on silica gel or were allowed to proceed until a qualitative UV spectrum of a

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