RELATIVE REACTIVITIES OF 2H-CYCLOPENTA[d]PYRIDAZINE AND THE 2-METHYL AND 2-PHENYL DERIVATIVES TO MONOCHLORINATION

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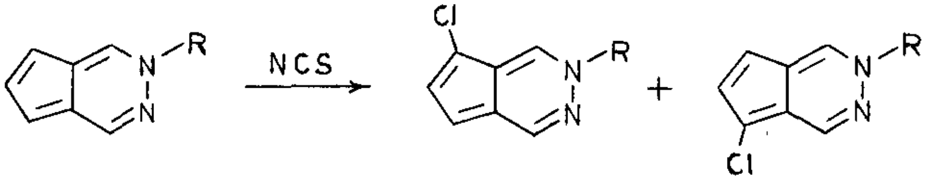
For electrophilic monochlorination with NCS, competitive reactions of pairs of the title compounds has shown the relative reactivities to be 7.1:1.7:1 for the 2-methyl, 2-phenyl, and 2-hydrogen compounds, respectively.

During studies of the electrophilic substitution reactions of 2*H*-cyclopenta[d]pyridazine (**1**) and its 2-methyl (**2**) and 2-phenyl (**3**) derivatives (1-4), it was noted that these compounds reacted at different rates. A study of the relative reactivities in the monotrifluoroacetylation reaction was carried out with milligram-scale, competitive-pair reactions with measurement of the product ratio by preparative TLC separation followed by purification and weighing of each component of the product mixture (5,6). This clearly established a reactivity order for this reaction of **2** > **3** > **1** and a ratio of *ca.* 5:2:1, respectively, but it was recognized that the losses in the separation and purification of the products and unchanged starting compounds were a source of error.

The subsequent purification and spectral characterization of the 5- and 7-monochloro derivatives (**4** - **8**)(3) permitted a more accurate determination of monochlorination product ratios from the known UV extinction coefficients. Product separation was effected with high pressure liquid chromatography. This method permitted (i) multiple product ratio analyses on each run, (ii) calibration by a mixture of known concentrations of starting compounds and products to check for possible loss on the column, and (iii) gravimetric analysis for comparison.



1, R=H
2, R=CH_3
3, R=C_6H_5

4, R=H
5, R=CH_3
6, R=C_6H_5

7, R-CH_3
8, R=C_6H_5

Although the direct comparison of the reactivities of 1, 2, and 3 by reaction of an equimolar mixture with 1 equiv. of NCS might have been possible, the complexity of the product mixture which would have resulted (7) led to the selection of two competitive-pair reactions: 2 *vs.* 1 and 2 *vs.* 3. Duplicate reaction runs were carried out with each pair and several chromatographic analyses were performed on each run. A gravimetric analysis and a calibration run were done for each pair.

With stirring, 40.9 mg (0.346 mmole) of 1 and 45.7 mg (0.346 mmole) of 2 were dissolved in 50 ml of CH_2Cl_2. A solution of 46.3 mg (0.346 mmole) of NCS in 50 ml of CH_2Cl_2 was added slowly and the mixture was stirred for 30 min. The solvent was removed (reduced pressure) below room temperature and the residual solids were dissolved in the minimum amount of CH_2Cl_2 to effect solution at 0 °C. The reaction of 2 and 3 with NCS was carried out in the identical manner and scale. A 5 μl sample of the final CH_2Cl_2 solution was injected onto a 0.125 in. x 6 ft. Corasil 2 column in a Waters Associates Model ALC-100 high pressure liquid chromatograph apparatus with the flow rate at 54 ml/hr. The elution solvent was 93% CH_2Cl_2 - 7% Et_2O for 1 and 4, 65% CH_2Cl_2 - 35% hexane for 2, 5, and 7, and 98% hexane - 2% Et_2O for 3, 6, and 8. Elution time was ca. 35 min. Each component (detected by a differential refractometer attachment) was collected separately in a 10 ml volumetric flask. The solvent was removed (N_2 stream), dry ether was added to the mark, the UV spectrum was recorded, and the amount of compound calculated.

For the reaction of 2 vs. 1, it was found that 85% of 2 and 12% of 1 had reacted (ratio of 7.1:1). For the reaction of 2 vs. 3, it was found that 77% of 2 and 18.5% of 3 had reacted (ratio of 4.2:1). The relative reactivities are, therefore, 7.1:1.7:1 for 2, 3, and 1, respectively.

Rate enhancement by the resonance effect is thus greater than rate depression by the inductive effect for the phenyl group.

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5 A. G. Anderson, Jr., and M. T. Wills, unpublished results. Qualitative comparison showed 2 to be ca. 250 times more reactive than azulene toward trifluoroacetic anhydride.

6 A mixture of 5- and 7-monosubstitution products was obtained from 2 and 3, but only the more stable 7- derivative was formed from 1.

7 The five monochlorination products (**4** - **8**) plus three unreacted starting compounds as compared with three monochlorination products (**4**, **5**, **7**) plus two starting compounds for **2** vs. **1** and four monochlorination products (**5** - **8**), plus two starting compounds for **2** vs. **3**.

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