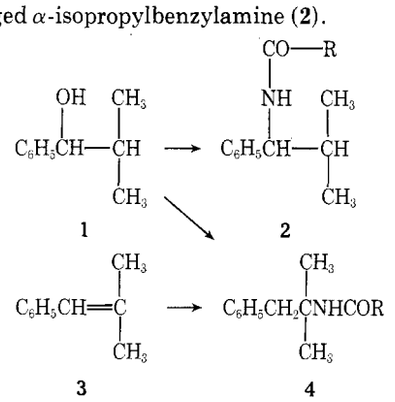
Molecular Rearrangements in the Course of Ritter Reactions

Susan Edwards and Fritz-Hans Marquardt*[1]

Research Department, Pharmaceutical Division, CIBA-GEIGY Corporation, Summit, New Jersey 07901

Received November 27, 1973

It is well known that the Ritter reaction occurs *via* ionic intermediates and that molecular rearrangements take place if the initial carbonium ion intermediate can isomerize to a more stable one.[2] Thus Boltze and Mühlenbein[3] reported that α-isopropylbenzyl alcohol (**1**) reacts with hydrogen cyanide or with nitriles under acidic conditions to yield amides of α,α-dimethylphenethylamine (**4**). On the other hand, this seems to contradict the report by Christol, *et al.*,[4] that Ritter reactions of **1** form amides of the unrearranged α-isopropylbenzylamine (**2**).



a, R = CH_3
b, R = C_6H_5

A check of the reaction conditions which were used by these two groups showed that a reasonable cause for this discrepancy could have been the different order of addition of reagents used, since this in turn could have easily changed the type of mechanistic factor which controlled the reactions. Thus, Boltze and Mühlenbein first mixed the carbinol and the acids, and only later added the nitrile, whereas Christol and coworkers first mixed the carbinol with the nitrile, and added the sulfuric acid last. In the first case, the initially formed carbonium ion may therefore have had ample time to rearrange into a more stable structure before the nitrile was added (*e.g.*, thermodynamic control of reaction), while in the second case the nitrile could trap the carbonium ions as they were being formed (*e.g.*, kinetic control). This would also explain Christol's additional observation that, while the Ritter reaction of **1** yielded **2**, the same reaction with the styrene derivative **3** only yielded **4**.

To check our rationalization, we only changed the order of addition of reagents when **1** was allowed to react with nitriles in a mixture of sulfuric and acetic acid under otherwise identical conditions. As was expected, **2** was obtained when sulfuric acid was the last reagent which was added, while **4** was obtained when the nitrile was added last.[5]

Experimental Section

Melting points were determined in capillaries and are uncorrected; nmr spectra were recorded on a Varian Associates A-60 spectrometer with TMS as internal standard.

α-Isopropylbenzyl Alcohol (1). To a refluxing suspension of 13 g (0.34 mol) of lithium aluminium hydride in 300 ml of tetrahydrofuran was added 100 g (0.675 mol) of isobutyrophenone (Aldrich) in 200 ml of tetrahydrofuran. After 2 hr of additional refluxing, the reaction mixture was cooled to room temperature and treated with 15 ml of water, 15 ml of 15% aqueous sodium hydroxide, and 39 ml of water. The suspension was filtered, the filter residue was washed thoroughly with 200 ml of tetrahydrofuran, and the solvent of the combined filtrates was evaporated under reduced pressure to yield 84.9 g of crude **1**, which was purified by fractionation over a Vigreux column and gave 73.9 g (0.526 mol, 78% of theory) of **1**, bp 77–78° (0.3 mm).

***N*-(α,α-Dimethylphenethyl)acetamide (4a).** To a solution of 6.0 g (0.04 mol) of compound **1** in 6.0 ml of glacial acetic acid and 3.3 ml of 95% sulfuric acid was added dropwise 1.9 g (0.046 mol) of acetonitrile at 70°, and the mixture was kept for an additional 1 hr at this same temperature. Then it was added to enough crushed ice to keep the resulting solution at room temperature, treated with 14 ml of 25% aqueous sodium hydroxide, returned just to acidic by addition of 15% aqueous sulfuric acid, and extracted in two steps with 150 ml of methylene chloride. The combined extracts were washed with 3 × 50 ml of water and dried over sodium sulfate and the solvent was evaporated under reduced pressure to yield 7.1 g of an oil, which crystallized in cyclohexane to give 2.7 g (0.014 mol, 35% of theory) of **4a**: mp 89–90° (lit.[3] mp 91–92°); nmr ($CDCl_3$) 2 CH_3 at 1.29 (s), CH_3 at 1.85 (s), CH_2 at 3.02 (s), C_6H_5 at 7.19 ppm (complex).

***N*-(α,α-Dimethylphenethyl)benzamide (4b).** By the method described for the preparation of **4a**, but using 3.3 g (0.032 mol) of benzonitrile instead of the acetonitrile, the crude product was 6.4 g of crystalline material which was purified by recrystallization in 95% ethanol: mp 109–110°; nmr ($CDCl_3$) 2 CH_3 at 1.43 (s), CH_2 at 3.14 (s), 10 aromatic at 7.1–7.8 ppm (complex).

Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.95; H, 7.33; N, 5.57.

***N*-(α-Isopropylbenzyl)acetamide (2a).** To a solution of 6.0 g (0.04 mol) of **1** and 1.9 g (0.046 mol) of acetonitrile in 6.0 ml of glacial acetic acid was added 3.3 ml of 95% sulfuric acid at 70°. After the previously described work-up, which yielded 6.6 g of crude product, a recrystallization in 2-propanol gave 2.6 g (0.0135 mol, 34% of theory) of **2a**: mp 114–116°; nmr ($CDCl_3$) CH_3 at 0.78 (d), CH_3 at 0.95 (d), CH_3 at 1.9 (s), CH at 1.9 (heptet), CH at 4.7 (broad triplet), C_6H_5 at 7.2 ppm (s).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.40; H, 8.96; N, 7.32. Found: C, 75.60; H, 8.56; N, 7.37.

***N*-(α-Isopropylbenzyl)benzamide (2b).** By the method described for the preparation of **2a**, but using 3.3 g (0.032 mol) of benzonitrile instead of acetonitrile, the crude product was 6.2 g of crystalline material, which was purified by recrystallization in ethanol: mp 139–140° (lit.[4] mp 141°); nmr ($CDCl_3$) CH_3 at 0.87 (d), CH_3 at 1.02 (d), CH at 2.23 (heptet), CH at 5.01 (broad triplet), 10 aromatic at 7.4–7.9 ppm (complex).

Acknowledgment. We wish to acknowledge the helpful discussions with Dr. J. L. Marsh and with Mr. L. Dorfman, whose staff we thank for microanalyses and spectra.

Registry No.—**1**, 611-69-8; **2a**, 33617-85-5; **2b**, 51310-27-1; **4a**, 5531-33-9; **4b**, 51310-28-2; isobutyrophenone, 611-70-1.

References and Notes

(1) To whom inquiries should be directed to Dyestuffs & Chemicals Division, CIBA-GEIGY Corp., P.O. Box 11422, Greensboro, N. C. 27409.
(2) For a recent review of this reaction see L. I. Krimen and D. J. Cota, *Org. React.*, **17**, 213 (1969).
(3) K.-H. Boltze and H. Muhlenbein, German Patent 1,144,713 (Oct 14, 1960).
(4) H. Christol, A. Laurent, and M. Mouseron, *Bull. Soc. Chim. Fr.*, 2313 (1961).
(5) The structure of the products was assigned unequivocally from their nmr spectra, since the chirality of the benzylic carbon of **2** gives diastereotopic character to its two methyl groups.

N-Acyllactam Rearrangements. The Fate of the Carboxyl Carbon and the Synthesis of 2-*tert*-Butyl-1-pyrroline

Bradford P. Mundy,* Kenneth B. Lipkowitz, Marc Lee, and Brent R. Larsen

Department of Chemistry, Montana State University, Bozeman, Montana 59715

Received February 5, 1974

The rearrangement of *N*-acyllactams to 2-substituted cyclic imines has recently been investigated in our labora-