JOC*Note*

Intervention of Phenonium Ion in Ritter Reactions

Tse-Lok Ho* and Rong-Jie Chein

Department of Applied Chemistry, National Chiao Tung University, Hsinchu, Taiwan, Republic of China

tlho@cc.nctu.edu.tw

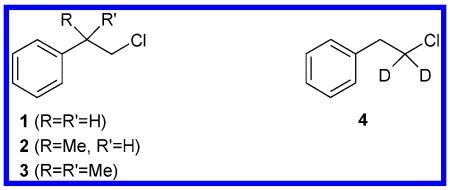
Received October 21, 2003

Abstract: The transformation of phenylethyl chloride to 3,4-dihydroisoquinolines is shown to proceed via phenonium ion. The evidence comes from a study of dideuterated analogue **4**, and the monomethylated and dimethylated compounds **2** and **3**.

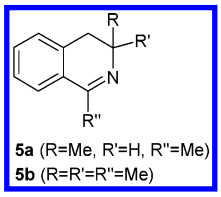
The Ritter reaction involves the generation of relatively stable carbocations from alcohols or alkenes and trapping of the cations in situ by nitriles to provide, after hydrolysis, amide products.[1−3]

In view of the structural requirements for the cationic precursors, we were intrigued by the report[4] of Lora-Tamayo et al. that describes the formation of 1-substituted-3,4-dihydroisoquinolines from reaction of 1-chloro-2-phenylethane **1** with cyanides in the presence of $SnCl_4$. These authors implicitly asserted an assisted ionization of the chloride to form *N*-(2-phenylethyl)nitrilium species, which rapidly cyclized (Scheme 1). In our opinion, this interpretation is tenuous and intervention of a phenonium ion[5,6] is more likely.

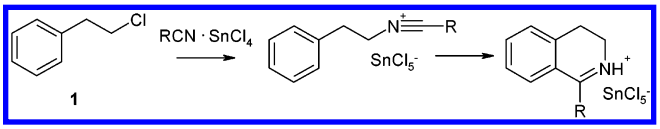
To verify our conjecture, we investigated the behavior of 1-chloro-2-phenylethane analogues **2** and **3** and the dideuterio derivative **4**.



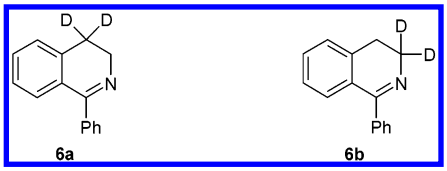
When **2** and **3** were submitted to the reaction conditions described by Lora-Tamayo et al., we obtained products corresponding to structure **5** only. Thus, the ^{13}C NMR spectrum of **5b** indicates the presence of a quaternary carbon atom that is attached to an amine nitrogen (δ 53.4) and NOE study showed a proximal relationship between a CH_2 (δ 2.63) and a peri-H (δ 7.07). Such effect



SCHEME 1



would not be observed for the alternative unrearranged product structure. Similar evidence was obtained for **5a**. These results indicate a rearrangement pathway for the formation of the dihydroisoquinolines and definitely rule out direct participation of the nitriles to assist departure of the chlorine atom. Accordingly, two possible mechanisms remain to be considered: a 1,2-aryl shift to give more stable carbocationic intermediates, or phenonium ion formation. To differentiate these possibilities, we prepared **4** from methyl phenylacetate via reduction with $LiAlD_4$ and conversion of the dideuterated alcohol to the chloride with $SOCl_2$. The reaction with PhCN·$SnCl_4$ gave a product that is shown to be a mixture of **6a** and **6b**.



The ^1H NMR spectrum displays a pair of signals at δ 2.71 and 3.76, and integration data suggest a 1:1 ratio within experimental error. Thus our results strongly argue for the intervention of a phenonium ion intermediate at least in the case of the parent substrate **1**, and indeed explain the peculiar reactivity of the 2-phenylethyl chlorides as contrary to other primary alkyl halides.[7]

Experimental Section

General Methods. NMR spectra were recorded with $CDCl_3$ as solvent, at 300 and 74 MHz respectively for ^1H and ^{13}C absorption. Chemical shifts are in ppm relative to 0 for TMS.

Formation of 3,4-Dihydroisoquinolines.[4] A mixture of chloride **1**, **2**, **3**, or **4** and MeCN or PhCN (2.1 mmol each) was placed in a flask fit with a rubber septum and a condenser, and $SnCl_4$ (2 mmol) was added through a syringe to the stirred mixture. After the exothermic reaction subsided, the mixture was heated in an oil bath at 110−130 °C for 3 h. It was cooled, basified with 20% NaOH, and extracted with ether. The ethereal layer was extracted with 20% HCl, neutralized with an aqueous solution with NaOH, and extracted with ether. On evaporation of the dried ethereal extract, 3,4-dihydroisoquinoline derivatives were obtained in 45−55% yield.

1,3-Dimethyl-3,4-dihydroisoquinoline[8,9] **(5a).** ^1H NMR δ 1.35 (3H, d, J = 6.6 Hz), 2.35 (3H, d, J = 2.1 Hz), 2.45 (1H, dd,

(1) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045−4048.
(2) Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213−325.
(3) Johnson, F.; Madronero, R. *Adv. Heterocycl. Chem.* **1996**, *6*, 95−146.
(4) Lora-Tamayo, M.; Madronero, R.; Munoz, G. G. *Chem. Ber.* **1960**, *93*, 289−297.
(5) Olah, G. A.; Porter, R. D. *J. Am. Chem. Soc.* **1971**, *93*, 6877−6887.
(6) Olah, G. A.; Spear, R. J.; Forsyth, D. A. *J. Am. Chem. Soc.* **1976**, *98*, 6284−6289.
(7) Meerwein, H.; Lasch, P.; Wersch, R.; Spille, J. *Chem. Ber.* **1956**, *89*, 209−224.
(8) Gray, N. M.; Cheng, B. K.; Mick, S. J.; Lair, C. M.; Contreras, P. C. *J. Med. Chem.* **1989**, *32*, 1242−1248.
(9) Grunewald, G. L.; Galdwell, T. M.; Li, Q.; Criscione, K. R. *Bioorg. Med. Chem.* **1999**, *7*, 869−880.

10.1021/jo035561y CCC: $27.50
Published on Web 12/30/2003

J = 15.6, 12.6 Hz), 2.71 (1H, dd, J = 15.6, 5.1 Hz), 3.48−3.57 (1H, m), 7.14 (1H, d, J = 7.2 Hz), 7.24−7.35 (2H, m), 7.46 (1H, d, J = 7.2 Hz); ^{13}C NMR δ 22.0 (q), 23.3 (q), 33.4 (t), 51.8 (d), 125.2 (d), 126.8 (d), 127.5 (d), 129.3 (s), 130.5 (d), 137.2 (s), 163.4 (s).

1,3,3-Trimethyl-3,4-dihydroisoquinoline[10−13] **(5b).** ^{1}H NMR δ 1.15 (6H, s), 2.32 (3H, s), 2.63 (2H, s), 7.07 (1H, d, J = 7.2 Hz), 7.20−7.28 (2H, m), 7.40 (1H, d, J = 7.8 Hz); ^{13}C NMR δ 23.1 (q), 27.8 (q), 38.6 (t), 53.4 (s), 125.0 (d), 126.5 (d), 127.9 (d), 128.4 (s), 130.4 (d), 136.1 (s), 161.0 (s).

1-Phenyl-3-methyl-3,4-dihydroisoquinoline[14] **(5a, R″ = Ph).** ^{1}H NMR δ 1.48 (3H, d, J = 6.9 Hz), 2.62 (1H, dd, J = 15.6, 12.3 Hz), 2.83 (1H, dd, J = 15.5, 4.9 Hz), 3.69−3.77 (1H, m), 7.29−7.61 (9H, m); ^{13}C NMR δ 21.6 (q), 33.4 (t), 52.7 (d), 126.4 (d), 127.3 (d), 127.5 (d), 127.8 (d), 128.0 (d), 128.4 (d), 128.5 (s), 128.8 (d), 129.1 (d), 130.6 (d), 138.4 (s), 138.9 (s), 166.2 (s).

1-Phenyl-3,3-dimethyl-3,4-dihydroisoquinoline[15] **(5b, R″ = Ph).** ^{1}H NMR δ 1.19 (6H, s), 2.72 (2H, s), 7.09∼7.47 (9H, m); ^{13}C NMR δ 27.5 (q), 38.8 (t), 54.5 (s), 126.4 (d), 127.9 (d), 128.1 (d), 128.2 (d), 128.4 (s), 128.7 (d), 128.9 (d), 129.0 (d), 130.7 (s), 137.5 (s), 164.6 (s).

Mixture of 1-Phenyl-3,3-dideuterio-3,4-dihydroisoquinoline (6b) and 1-Phenyl-4,4-dideuterio-3,4-dihydroisoquinoline (6a). ^{1}H NMR δ 2.71, 3.76 (1:1) (2H, s), 7.16−7.54 (9H, m)

Acknowledgment. This research was generously supported by the National Science Council, Republic of China.

JO035561Y

(10) Shklyaev, V. S.; Aleksandrov, B. B.; Legotkina, G. I.; Vakhrin, M. I.; Gavrilov, M. S.; Mikhailovskii, A. G. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1983**, *19*, 1242.

(11) Dautova, R. Z.; Shklyaev, V. S.; Syropyatov, B. Ya.; Aleksandrov, B. B.; Mikhailovskii, A. G.; Vakhrin, M. I. *Pharm. Chem. J. (Engl. Transl.)* **1989**, *23*, 133−136.

(12) Mikhal'chuk, A. L.; Gulyakevich, O. V.; Shklyaev, Yu. V.; Shklyaev, V. S.; Akhrem, A. A. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1998**, *34*, 602−610.

(13) Balebanova, E. V.; Davydov, V. V.; Zorin, A. N.; Syropyatov, B. Ya. *Pharm. Chem. J. (Engl. Transl.)* **1996**, *30*, 507−509.

(14) Whaley, W. M.; Hartung, W. H. *J. Org. Chem.* **1949**, *14*, 650−651.

(15) Seeger, E.; Engel, W.; Teufel, H.; Machleidt, H. *Chem. Ber.* **1970**, *103*, 1674−1676.