A ONE-POT ISOQUINOLINE SYNTHESIS BY CYCLODEHYDROGENATION OF BENZYLAMINOACETALS WITH CHLOROSULFONIC ACID[1]

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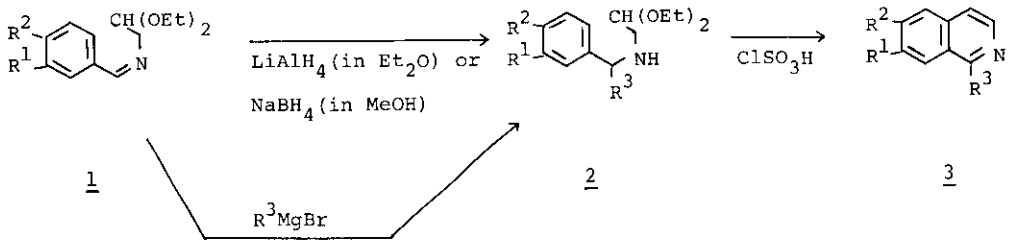
Abstract —— A direct preparation of the fully aromatized isoquinolines (3*a*-*l*) by the cyclodehydrogenation of benzylaminoacetals (2*a*-*l*) with chlorosulfonic acid is described.
Comparing the behavior of chlorosulfonic acid with that of sulfuric acid toward 1,2-dihydroisoquinoline, it is able to be suggested that benzylaminoacetals were cyclized first to 1,2-dihydroisoquinolines, subsequently, dehydrogenated to the fully aromatized isoquinolines by the hydride abstraction with $ClSO_3H$. Substitution by a larger R^3 group than isopropyl in the acetal $ArCH(R^3)NHCH_2CH(OEt)_2$, interfered this second step, so the corresponding isoquinolines could not be obtained.

The standard Pomeranz-Fritsch reaction[2] is one of the most convenient methods for direct preparation of fully aromatized isoquinolines, but certain benzylideneaminoacetals react with difficulty or not at all. Thus, isoquinoline (3*a*) itself is obtained only less than 5% yield from benzylideneaminoacetal (1*a*). An attempt to cyclize 3,4-dimethoxy substrate (1*e*) has failed to yield the anticipated isoquinoline (3*e*)[3]. Therefore, 3*e* has been prepared by dehydrogenation of the hydroisoquinolines (3,4-dihydro and 1,2,3,4-tetrahydro[4a]) and their derivatives[4b] indirectly, or by treatment of the reduced benzylideneaminoacetal (2*e*) with sulfuric acid *containing an oxidizing agent* such as arsenic pentoxide[3,5], or by elegant cyclization of N-tosyl-3,4-dimethoxybenzylaminoacetal in boiling HCl-dioxane system[6]. Another slight modification of this reaction was provided by Popp and McEwen[7] who showed that when 1*e* was stirred in a mixture of $POCl_3$ and polyphosphoric acid at room temp., 3*e* was produced in a moderate yield (53%).
We now wish to report a one-pot preparation of the fully aromatized isoquinolines (3*a*-*l*) by the cyclodehydrogenation of benzylaminoacetals (2*a*-*l*) with $ClSO_3H$ *without adding any other oxidizing agent*.



a: $R^1=R^2=R^3=H$
b: $R^1=OCH_3$, $R^2=R^3=H$
c: $R^1=R^2=OCH_3$, $R^3=H$
d: $R^1=R^2=H$, $R^3=CH_3$
e: $R^1=OCH_3$, $R^2=H$, $R^3=CH_3$
f: $R^1=R^2=OCH_3$, $R^3=CH_3$
g: $R^1=R^2=H$, $R^3=CH_2CH_3$
h: $R^1=OCH_3$, $R^2=H$, $R^3=CH_2CH_3$
i: $R^1=R^2=OCH_3$, $R^3=CH_2CH_3$
j: $R^1=R^2=H$, $R^3=CH_2CH_2CH_3$
k: $R^1=OCH_3$, $R^2=H$, $R^3=CH_2CH_2CH_3$
l: $R^1=R^2=OCH_3$, $R^3=CH_2CH_2CH_3$

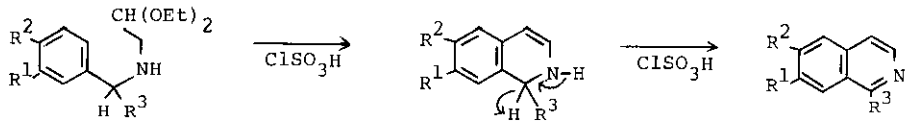
One equiv. of benzylaminoacetals (2) prepared readily by $LiAlH_4$ or $NaBH_4$ reduction of 1, or by the addition[8] of Grignard reagents to the appropriate Schiff bases (1), was added slowly to ten equivs. of chilled $ClSO_3H$ (- 10°) under nitrogen atmosphere, followed by standing at range from room temp. (for 72 h with the reactive substrates such as 2*b*, 2*c*, 2*e*, 2*f*, 2*h*, 2*i*, 2*k*, and 2*l*) to 100° (for 5-10 min with the unreactive acetals such as 2*a*, 2*d*, 2*g*, and 2*j*). The reaction mixture was poured onto crushed ice. After removal of neutral substance by shaking with Et_2O, the acidic solution was made alkaline with Na_2CO_3. The basic constituent was extracted with CH_2Cl_2. The crude base thus obtained was subjected to gas chromatography. Only one peak was recognized except for two cases (2*h* → 3*h* and 2*k* → 3*k*)[9]. All of the known (3*a*-*g*, 3*i*, 3*j*, and 3*l*) and new bases (3*h* and 3*k*) obtained by this one-frask operation were shown to be identical with the corresponding authentic specimens prepared by the alternative well known methods. Various spectral, especially, UV absorption curves of these bases were rational for the fully aromatic structures[10].

The yields (%) of the products (3) based upon the substrates (2) are as follows: *a*,53; *b*,26; *c*,48; *d*,75; *e*,27; *f*,54; *g*,63; *h*,16; *i*,29; *j*,47; *k*,15; *l*,18.

Since a similar procedure using conc. H_2SO_4 instead of $ClSO_3H$ has result only in resinification, it has been suggested that $ClSO_3H$ plays not only a role of the same cyclizing action in the Pomeranz-Fritsch reaction, but also a dehydrogenating action in an intermediate stage to form the fully aromatic end-product.

To probe this capability the following experiments were carried out. 1,2-Dihydroisoquinoline[11] was added to $ClSO_3H$ at - 15° under nitrogen atmosphere, followed by keeping at the same temp. for 1 h or by heating at 100° for 5-10 min to give *3a* with almost quantitative yield. Whereas treatment of it with conc. H_2SO_4 leads to a resinous substance insoluble in dilute acid.

The direct formation of isoquinolines from benzylaminoacetals with $ClSO_3H$ which we have observed, can be rationalized by a possible mechanism as shown here.



2 *3*

Because the substrates, $ArCH(R^3)NHCH_2CH(OEt)_2$ having a bulkier alkyl group R^3 than isopropyl fail to give the desired isoquinolines, such a large substituent appears to interfere the process of building up the fully aromatic skeleton by $ClSO_3H$ in this reaction.

Physical and Spectral Data of the New Substrates

2f: bp 199-200°/5 torr; MS (*m/e*, M^+) 297.

2h: bp 215-217°/5 torr; MS (*m/e*, M^+) 253.

2i: bp 206-209°/5 torr; MS (*m/e*, M^+) 311.

2j: bp 178-179°/5 torr; MS (*m/e*, M^+) 265.

2k: bp 242-245°/5 torr; MS (*m/e*, M^+) 295.

2l: bp 249-250°/5 torr; MS (*m/e*, M^+) 325.

Physical and Spectral Data of the New Bases

3h: bp 148-150°/5 torr; MS (*m/e*, M^+) 187; UV λ_{max}^{MeOH} nm (*log* ε) 235(3.68), 266(3.41), 271(3.38), 328(3.28), 338(3.32).

3k: bp 198-200°/3 torr; MS (*m/e*, M^+) 201; UV λ_{max}^{MeOH} nm (*log* ε) 234(4.52), 271(4.19), 288(4.04), 322(3.39), 332(3.42).

References and Notes

1. Part 3 in the series "Halosulfonic Acid as a Cyclizing Agent for Isoquinoline Synthesis", Part 2, K. Kido and Y. Watanabe, *Yakugaku Zasshi*, 1975, **95**, 1038.
2. W. J. Gensler, *"Organic Reactions"*, Vol. 6, ed. by R. Adams, John Wiley & Sons Inc., New York, N.Y., 1951, pp. 191-206.
3. L. Rügheimer and P. Schön, *Chem. Ber.*, 1909, **42**, 2374.
4. a) E. Späth and N. Polgar, *Monatsh. Chem.*, 1929, **51**, 190; P. A. Wehrli and Schaer, *Synthesis*, 1974, 288: b) B. Umezawa, O. Hoshino, and S. Sawaki, *Chem. Pharm. Bull.*, 1969, **17**, 1115; S. V. Kessar, Y. P. Gupta, A. Gainda, and A. Varsa, *Indian J. Chem.*, 1978, **16B**, 319.
5. R. Forsyth, C. I. Kelly, and F. L. Pyman, *J. Chem. Soc.*, 1925, **127**, 1659.
6. A. J. Birch, A. H. Jackson, P. V. R. Shannon, and P. S. P. Varma, *Tetrahedron Letters*, 1972, 4789; b) idem, *J. Chem. Soc. Perkin I*, 1974, 2185; c) idem, *ibid.*, 1974, 2190.
7. F. D. Popp and W. E. McEwen, *J. Am. Chem. Soc.*, 1957, **79**, 3773.
8. N. Vinot and R. Quelet, *Bull. Soc. Chim. France*, 1959, 1164; P. Lejay and C. Viel, *Ann. Chim. Paris*, 1977, **2**, 87.
9. Monochloro derivatives of parent bases (3*h* and 3*k*) were obtained as by-products in extremely low yield. Their formulas are shown as $C_{12}H_{12}ClNO$ (*m/e*, M^+ 221) and $C_{13}H_{14}ClNO$ (*m/e*, M^+ 235) by MS.
10. L. Hruban, F. Šantavý, and S. Hegerová, *Collection Czech. Chem. Commun.*, 1970, **35**, 3420.
11. L. M. Jackman and D. I. Packham, *Chem. & Ind.*, 1955, 360.

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