A SIMPLE EFFICIENT SYNTHESIS OF A NEW, VERSATILE TETRAHYDRO-ISOQUINOLINE-1,3-AMINOALCOHOL SYNTHON[1,2]

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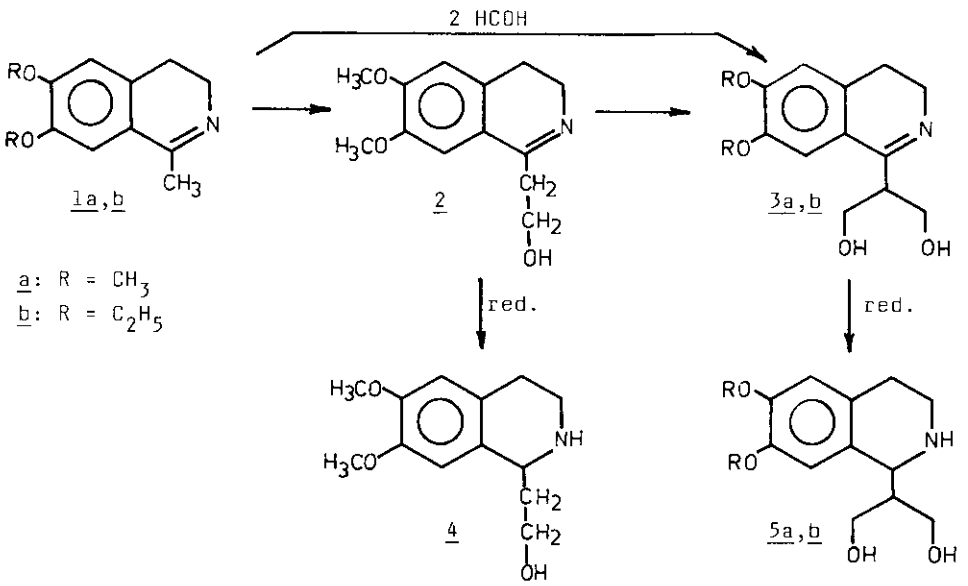
Abstract - Through the addition of 2 moles of formaldehyde to 1-methyl-6,7-dimethoxy- and 6,7-diethoxy-3,4-dihydroisoquinoline, the corresponding 1-[bis(hydroxymethyl)methyl]-6,7-dialkoxy-3,4-dihydroisoquinolines (3a,b) were prepared, which were then reduced to the 1,3,3'-trifunctional tetrahydroisoquinoline aminoalcohol synthons (5a,b).

We earlier reported the synthesis of several new 1,3-heterocycles angularly fused with the tetrahydroisoquinoline skeleton.[3,4] This paper describes a convenient, rapid, low-cost preparation of a new, versatile trifunctional tetrahydroisoquinoline synthon[5] (5), containing a 1,3-aminoalcohol structural unit. Compound 5 has been used as starting material in the synthesis of numerous classes of valuable pharmacologically active compounds containing an isoquinoline moiety.[6-8]

Though the reactivity of the methyl group of 1-methyl-3,4-dihydroisoquinoline is well known,[9] surprisingly its reaction with formaldehyde has yet not been reported. On the other hand, the reactions with formaldehyde of other isoquinoline derivatives containing an active methylene group, such as 1-*ethoxycarbonylmethyl-* or 1-cyanomethyl-3,4-dihydroisoquinolines, have been thoroughly investigated.[10,11] The addition of formaldehyde to 1-methylisoquinoline has also been reported,[12] but in this reaction 1-[bis(hydroxymethyl)methyl]isoquinoline was obtained in only 60% yield.

We have found that 1-methyl-3,4-dihydro-6,7-dialkoxyisoquinoline (1) readily reacts with formaldehyde under mild conditions in a base-catalysed reaction. At a 1:1 molar ratio of the reaction partners, the unchanged starting material was accompanied by the single (2) and double (3) formaldehyde adducts. With a 50% excess of formaldehyde, the reaction of the starting isoquinoline derivative was complete, but gave a mixture of 2 and 3. For R = CH_3, these components were separated by fractional crystallization. The structure of 2 was confirmed by catalytic reduction to homocalycotomine (4).[13]

With two equivalents or more of formaldehyde, 1 furnished compound 3 as the sole product. The intermediate 2 could also be transformed to 3 with a formaldehyde excess. The yield of 3 was influenced considerably by the solvent; the highest yields were obtained in methanol. The optimum reaction time at room temperature was 6-7 h, while at the boiling point of methanol it was 30 min. Prolonged refluxing resulted in the formation of considerable amounts of decomposition products.



Compounds 3a,b undergo facile reduction catalytically or with sodium borohydride, to the corresponding 1,2,3,4-tetrahydroisoquinolines (5a,b). The trifunctional 1,3-aminoalcohol derivative 5, readily obtainable by this procedure, exhibits promising pharmacological effects,[5] and is a convenient, versatile synthon for the preparation of further derivatives interesting from both chemical and pharmacological[6-8] aspects.

EXPERIMENTAL

Reaction of 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline (1a) with formaldehyde

Method A - Compound 1a[14] (20.5 g; 0.1 mol) was dissolved in methanol (120 ml), and 10% sodium hydroxide (1 ml) and then 36% formaldehyde (12.5 ml; 0.05 mol) were added to the solution. After refluxing for 30 min, the solution was evaporated to dryness and the residue was with ether (3x200 ml). The insoluble remainder was crystallized from a mixture of acetone and ether to give compound 3a (12 g; 45%), mp 130-132 °C. Evaporation of the ethereal solution and repeated recrystallization from ether afforded 2a (8 g; 34%), mp 105-107 °C.

Method B - Proceeding as described under Method A, but using 21 ml (0.25 mol) of formaldehyde, refluxing for 30 min or stirring at room temperature for 6-7 h gave, after evaporation, a product which was recrystallized from benzene.

Method C - Compound 1[14,15] (0.5 g; 0.1 mol) was added to a stirred suspension of paraformaldehyde (8 g; 0.25 mol) in methanol (100 ml). Freshly prepared sodium ethoxide (0.15 g of sodium in 5 ml of ethanol) was added dropwise to the suspension until a light-yellow, homogeneous solution was obtained. After stirring for 6 h at room temperature, the reaction mixture was evaporated to dryness to yield compound 3 as a crystalline product.

Method D - A solution of compound 2 (1.18 g; 5 mmol) in methanol (10 ml) was refluxed with 37% aqueous formaldehyde (1 ml) for 1 h. Evaporation of the reaction mixture gave crystalline 3a.

Reduction of the 1-[bis(hydroxymethyl)methyl]-3,4-dihydro-6,7-dialkoxyisoquinolines (3a,b)

Method E - The dihydroisoquinoline 3 (0.1 mol) was dissolved in methanol (150 ml), the solution was cooled in ice-water and, with stirring, sodium borohydride (10.2 g; 0.3 mol) was added in small portions. Stirring was continued for 3 h at room temperature, the solution was then evaporated and the residue was dissolved in water (100 ml) and extracted with chloroform (3x100 ml). After drying, concentration of the organic phase gave the tetrahydroisoquinoline 5 as a crystalline product.

Method F - The dihydroisoquinoline 3 (2 mmol) was dissolved in methanol (100 ml) and reduced in a hydrogen atmosphere in the presence of platinum-on-activated-carbon catalyst (0.1 g; platinum content 5%), under normal (N.T.P.) conditions. After the calculated amount of hydrogen had been absorbed (1.5 h), the catalyst was removed by filtration. Evaporation of the reaction mixture gave the crystalline tetrahydroisoquinoline 5.

Method G - When the reaction was carried out as described under Method F, but using palladium-on-charcoal (0.1 g; Pd content 10%) instead of platinum, completion of the hydrogen absorption required 5 h.

Table Isoquinoline-1,3-aminoalcohols (2, 3a,b, 5a,b)

Compound	Yield[a] (%)	Mp[b] (°C)	Solvent		Analysis (%) Calcd./Found C	H	N	IR (KBr) (cm^{-1})
2	34 (A)	105-107	ether	$C_{13}H_{17}NO_3$ (235.28)	66.36 66.18	7.28 7.16	5.95 5.67	3170, 1620 1270, 1060
3a	45 (A) 88 (B) 95 (C) 84 (D)	130-132	acetone/ether	$C_{14}H_{19}NO_4$ (265.30)	63.38 63.28	7.22 7.33	5.28 5.17	3340, 1630 1280, 1045
3b	82 (B) 90 (C)	112-114	benzene	$C_{16}H_{23}NO_4$ (293.35)	65.51 65.48	7.90 8.22	4.78 4.69	3340, 1625 1280, 1050
5a	82 (E) 94 (F) 91 (G)	139-141	benzene/ether	$C_{14}H_{21}NO_4$ (267.32)	62.90 62.66	7.92 7.92	5.24 5.12	3300 1265, 1045
5b	77 (E) 89 (F)	127-128	benzene	$C_{16}H_{25}NO_4$ (295.37)	65.06 64.95	8.53 8.58	4.74 4.58	3320 1265, 1055

[a]The letter in brackets denotes the method used. [b]Mp's of the hydrochlorides (from ethanol/ether): 3a 181-184 °C; 3b 134-142 °C; 5a 218-220 °C; 5b 199-201 °C.

REFERENCES

1. Presented at the Tenth International Congress of Heterocyclic Chemistry, Waterloo (Canada), August 11-16, 1985. Proc. P8-221.
2. Part 101 of the series: Saturated Heterocycles; Part 100. G. Bernáth, F. Fülöp, G. Csirinyi and S. Szalma, Monatsh., accepted for publication (17 January, 1986).
3. F. Fülöp, M. S. El-Gharib, A. Sohajda, G. Bernáth, J. Kóbor and G. Dombi, Heterocycles, 1983, 20, 1325.
4. J. Kóbor, F. Fülöp, M. S. El-Gharib and G. Bernáth, J. Heterocyclic Chem., 1984, 21, 149.
5. G. Bernáth, J. Kóbor, F. Fülöp, E. Ezer, Gy. Hajós, É. Pálosi, L. Dénes and L. Szporny, Eur. Pat. 143,333; Chem. Abstr., 1985, 103, 215202.
6. G. Bernáth, J. Kóbor, F. Fülöp, G. Motika, A. Sohajda, E. Ezer, Gy. Hajós, É. Pálosi, L. Dénes and L. Szporny, Japan Kokai Pat., 60,109,567; Chem. Abstr., 1985, 103, 196018.
7. G. Bernáth, F. Fülöp, J. Kóbor, A. Kálmán, P. Sohár, E. Ezer, Gy. Hajós, L. Dénes, L. Szporny and É. Pálosi, Ger. Pat., 3,439,157; Chem. Abstr., 1985, 103, 160404.
8. G. Bernáth, J. Kóbor, F. Fülöp, P. Sohár, P. Perjési, E. Ezer, Gy. Hajós, É. Pálosi, L. Dénes and L. Szporny, Ger. Pat., 3,439,131; Chem. Abstr., 1985, 103, 160523.
9. G. Grethe, Isoquinolines, Part 1. In the series Chemistry of Heterocyclic Compounds, Vol. 38 (Eds.: A. Weissberger, E. C. Taylor), John Wiley, New York, 1981. p. 120.
10. R. F. K. Meredith, A. C. Ritchie, T. Walker and K. D. E. Whitting, J. Chem. Soc., 1963, 2672.
11. K. Harsányi, P. Kiss and D. Korbonits, J. Heterocyclic Chem., 1973, 10, 435.
12. R. Huisgen, H. Seidl and J. Wulff, Chem. Ber., 1969, 102, 915.
13. L. Dubravkova, I. Jezo, P. Sevcovic and Z. Voticzky, Chem. Zvesti, 1959, 13, 16; Chem. Abstr., 1959, 53, 17162e.
14. G. Bernáth, K. Koczka, J. Kóbor, L. Radics and M. Kajtár, Acta Chim. Acad. Sci. Hung., 1968, 55, 331.
15. M. B. Moore, H. B. Wright, M. Versten, M. Freifelder and R. K. Richards, J. Am. Chem. Soc., 1954, 76, 3656.

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