A NEW ONE-POT SYNTHESIS OF 1-ARYLMETHYL-1,2,3,4-TETRAHYDRO-ISOQUINOLINE DERIVATIVES FROM ISOQUINOLINIUM SALTS

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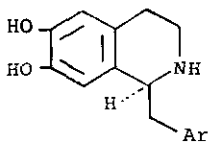
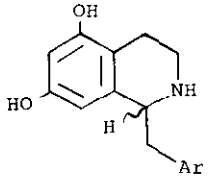
Abstract ——— There has been described a new one-pot synthesis of 1-arylmethyl-1,2,3,4-tetrahydroisoquinoline derivatives by the Barbier reaction of the quaternary salt (4) with various arylmethyl halides followed by reduction with sodium monoacetoxyborohydride.

1-Arylmetnyl-1,2,3,4-tetrahydroisoquinoline derivatives are known to exhibit β-adrenoceptor activity, as exemplified by trimetoquinol (TMQ), a clinically effective bronchodilator.[1)]



Trimetoquinol (TMQ)



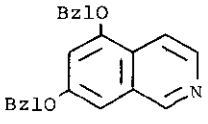
(1)

Ar=3,4,5-trimethoxyphenyl

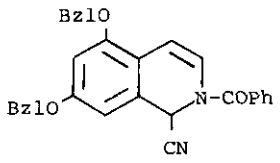
In the preceding paper,[2)] we reported the syntheses and β-adrenoceptor activities of five positional isomers of TMQ with respect to its 6,7-dihydroxyl groups, in which the 5,7-dihydroxy derivative (1) showed more potent activity and longer duration of action than (±)-TMQ on intraduodenal administration.

This finding prompted us to the structural modification of 1 by replacing the 3,4,5-trimethoxybenzyl group at the 1-position with other arylmethyl groups.

Previously, the compound (1) was prepared from the isoquinoline (2) in several steps involving alkylation of the Reissert compound (3) in 40% overall yield.

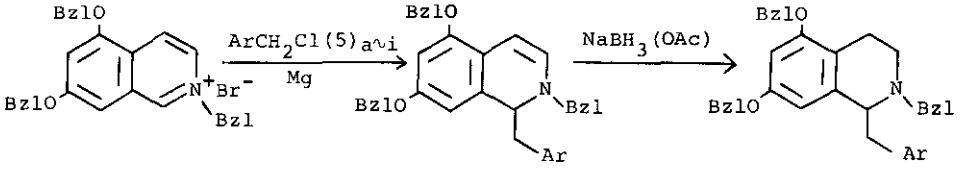


(2)



Bzl:Benzyl (3)

During the course of our study for a more convenient synthetic route to the derivatives of 1, we found a one-pot synthesis of 1-arylmethyl-1,2,3,4-tetrahydroisoquinolines $(7)_{a\sim i}$ by the Barbier reaction[3] of the quaternary salt (4) with arylmethyl halides followed by reduction with sodium monoacetoxyborohydride.



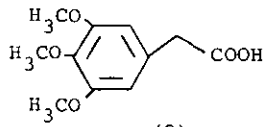
(4) $(6)_{a\sim i}$ $(7)_{a\sim i}$

a; Ar=3,4,5-trimethoxyphenyl
b; Ar=4-methoxyphenyl
c; Ar=3,4-dimethoxyphenyl
d; Ar=2,3,4-trimethoxyphenyl
e; Ar=3-benzyloxy-4-methoxyphenyl
f; Ar=3-methoxy-4-benzyloxyphenyl
g; Ar=3,4-dibenzyloxyphenyl
h; Ar=3,5-dibenzyloxyphenyl
i; Ar=α-Naphthyl

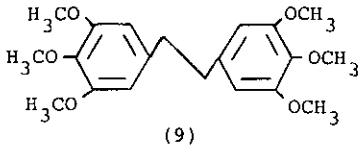
In 1954, Bradley and Jeffery reported that the addition of alkyl Grignard reagents to 2-alkylisoquinolinium salts gave 1-alkylated 1,2-dihydroisoquinoline derivatives.[4] As is well known, however, reaction of arylmethyl halides with

magnesium under the usual conditions tends to produce Wurtz-type condensation products.[5]

For instance, in our hands, the reaction of 3,4,5-trimethoxybenzyl chloride $(5)_a$ with magnesium[6] in tetrahydrofuran at room temperature for 1 h followed by quenching the Grignard mixture with carbon dioxide gave the phenylacetic acid (8) (mp. 116-118°) in only 21% yield, the dimer (9) (mp. 138-139°) being a major product (59%).



(8)



(9)

Therefore, we examined the Barbier reaction of the quaternary salt (4) with the halide $(5)_a$ in order to minimize the formation of the dimer (9).

Treatment of 5a (1.4 mmoles) with magnesium (1.5 m atoms) in refluxing tetrahydrofuran *in the presence of* 4 (1 mmole) gave the 1,2-dihydroisoquinoline $(6)_a$ [pale yellow viscous oil, MS *m/e*: 613(M^+)] in an excellent yield. Without purification, 5a was reduced with sodium borohydride (15 mmoles) in refluxing MeOH containing a small amount of water or by catalytic hydrogenation on PtO_2 in tetrahydrofuran to afford the tetrahydroisoquinoline $(7)_a$ [colorless needles, mp 104-106°, MS *m/e*: 615(M^+)] in 83% or 73% yields from 4, respectively.

Thus, the Barbier method was found to be much more superior to the Grignard method for the preparation of 1-arylmethyl-1,2,3,4-tetrahydroisoquinolines.

Next examined was direct reduction of the intermediate 1,2-dihydroisoquinolines $(6)_{a\sim i}$ with metal hydride without isolation.

Recently, we reported that sodium monoacyloxyborohydride [$NaBH_3OCOR$] reduces effectively various functional groups (e.g. carboxamides, carbamates, or nitriles) to the corresponding amines in non-hydroxylic solvents such as tetrahydrofuran or dioxane.[7]

Thus, the tetrahydrofuran solution of the Barbier mixture containing the intermediates $(6)_{a\sim i}$ was treated with 6equiv. of sodium monoacetoxyborohydride under reflux for 1-2 h to afford the corresponding tetrahydroisoquinolines $(7)_{a\sim i}$ in high yields. The results are summarized in Table I.

Table I. Barbier Reaction of the Quaternary Salt (4) with Various Arylmethyl Halides followed by Reduction with Sodium Monoacetoxyborohydride

Compound	Yield(%)	mp(dec.)	Salt	M^+ *m/e*
7a	92	132-136°	$HCl \cdot 1/2H_2O$	615
7b	86	171-172°	$(COOH)_2$	555
7c	86	154-156°	$1/2(COOH)_2 \cdot 1/2MeOH$	585
7d	83	122-125°	$(COOH)_2$	615
7e	84	185-187°	$(COOH)_2$	661
7f	88	185-186°	$(COOH)_2$	661
7g	89	171-172°	$(COOH)_2$	737
7h	84	176-177°	$(COOH)_2 \cdot 1/2MeOH$	737
7i	93	184-185°	$(COOH)_2$	575

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