SYNTHESES OF BIOLOGICALLY ACTIVE 4-ARYL-1,2,3,4-TETRAHYDROISOQUINOLINE DERIVATIVES UNDER CONTROL OF THE ORIENTATION OF POLONOVSKI REACTION

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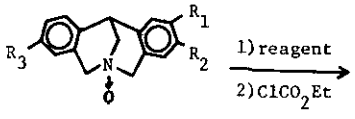
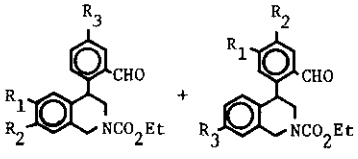
Although the synthetic utility of Polonovski reaction has been widely explored, a little has been known about the theory of the orientation of this reaction and much less the control of the orientation for synthetic methodology has been made. Thus, by using readily accessible 6,12-methano-dibenz[c,f]azocine N-oxides(1) substituted at suitable positions on aromatic rings, the orientation of Polonovski-type reaction was investigated in some details.

Reaction of 1a with $(CF_3CO)_2O$ followed by treatment with ClCOOEt/2N-Na_2CO_3 gave 2-carboethoxy-4-(o-formylphenyl)-1,2,3,4-tetrahydroisoquinoline(2a) in 95% yield. On the other hand, heating of 1a with t-BuOK in t-BuOH and subsequent treatment with 2N-HCl/ClCOOEt afforded 2a in 85% yield.

Reactions of unsymmetrical N-oxide(1b) with several reagents such as $(CH_3CO)_2O$, CH_3COCl, $(CF_3CO)_2O$, $(CF_3SO_2)_2O$, and t-BuOK(followed by the procedure described above) were carried out and the main result (isomer ratios and total yields) is shown in the Table. The result suggested that the variable-E2 transition state theory could be applied to this Polonovski-type reaction and that the orientation of this reaction could be controlled by the reaction conditions employed.

Application of this method to the related compound(1c) enabled (±)-cherylline, Amaryllidaceae alkaloid, to be synthesized. Thus, the reaction of 1c with t-BuOK in t-BuOH and subsequent treatment with ClCOOEt/2N-Na_2CO_3 provided 2c in 64% yield (2c'; only 9%). The formyl group of 2c was removed with $RhCl(PPh_3)_3$ in refluxing toluene to give 3 in 84% yield and subsequent reduction with $LiAlH_4$ afforded O,O-dibenzylcherylline(4) in 75% yield.

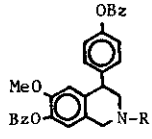




1a: $R_1=R_2=R_3=H$
1b: $R_1=OMe$, $R_2=R_3=H$
1c: $R_1=OMe$, $R_2=R_3=OBz$

2a
2b
2c

2b'
2c'



3: R=CO_2Et
4: R=Me

Table Reaction of 1b

reagent	ratio of 2b : 2b'	yield(%)
t-BuOK/t-BuOH	8 : 1	80
$(CF_3CO)_2O$	1 : 1	95
$(CF_3SO_2)_2O$	1 : 5	89