Pergamon

Tetrahedron Letters 39 (1998) 9427–9430

TETRAHEDRON LETTERS

Boron Trifluoride Promoted Addition of Aryllithiums to Estrone Benzyl Ether

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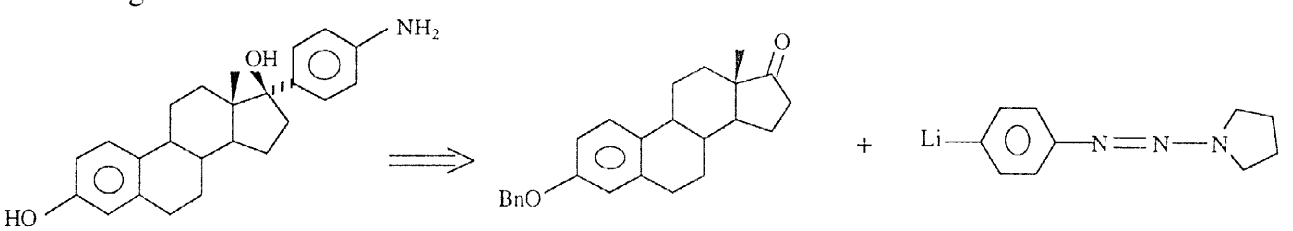
Received 2 September 1998; accepted 13 October 1998

Abstract : aryllithiums did not condense with estrone benzyl ether at low temperature. The promoted addition with boron trifluoride etherate was the best method for preparing substituted 17α-arylestradiols.

Modified steroids are challenging both in terms of chemical methodologies and biological potential. Estradiol derivatives substituted at the 11β or 17α positions may for example present antiestrogenic activities or be used as affinity markers[1-3]. Rigid substituents at the 17α position of estradiol are compatible with maintenance of a high level of recognition and the corresponding steroids may be potential imaging agents[4]. The synthesis of 17α-(4-aminophenyl)estradiol, **1**, was then considered in order to link an organometallic complex on nitrogen for the preparation of new radiopharmaceuticals. 17α-phenylestradiol, the only known 17-arylestradiol so far, has been previously prepared by addition of large excess of phenyllithium to estrone[5] or to a protected estrone [6] with weak to moderate yields. On the other hand, Gross et al. have recently described a methodology for the addition of N-protected aminophenyllithiums to ketones[7]. The retrosynthetic scheme of Fig. 1 could then be envisaged :



1 **2** **3**

Fig. 1

Owing to the poor solubility of estrone benzyl ether (EBE), **2**, in ether, the aryllithium, **3**, has been prepared in THF, by halogen-metal exchange between the corresponding bromo compound and sec-BuLi (2.2 eq. sec-BuLi at -78°C for 0.25h). EBE did not condense with **3** in these conditions. We present here a way to solve this problem and to synthesize the first 17α substituted phenyl estradiol derivatives.

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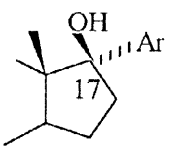
0040-4039/98/$ - see front matter
PII: S0040-4039(98)02185-6

In view of the previous failure, we have reconsidered the reaction of aryllithiums with EBE by using different activation methods : added $LiClO_4$ [8], use of an organocerium reagent, prepared from organolithium and anhydrous $CeCl_3$ [9,10], or an organotitanium compound, prepared with $TiCl_4$ [11,12]. The promoted organolithium addition by boron trifluoride etherate was also tried, which had been used for various reactions with electrophiles like epoxides and oxetanes[13,14], carboxylic anhydrides[15], or more recently oxime ethers[16] and imines[17]. Table 1 summarizes the results obtained for reaction of aryllithium **3** or PhLi (as model aryllithium) with EBE by use of different modes of activation. The percentage of addition product **4** was based on NMR ^1H spectrum of the rough product obtained after hydrolysis. Two singlets were respectivly observed for the benzylic protons (O-CH_2-Ph) of **4** and unreacted EBE and for the CH_3-18 groups of these two products (a typical value of 1.08 ppm was observed for the 17α-arylestradiols).

Table 1. n ArLi + EBE $\xrightarrow{\text{activation}}$  **4**

entry	ArLi	n	activation	solvent	T°C	t (h)	% **4**
1	**3**	2.6	$LiClO_4$	THF	-70	3	50
2	"	"	BF_3	"	-85	"	57
3	PhLi	2.7	"	"	-82	2	60
4	"	2	$CeCl_3$	"	-80	3	14
5	"	2.2	$TiCl_4$	mixed	-40	"	0

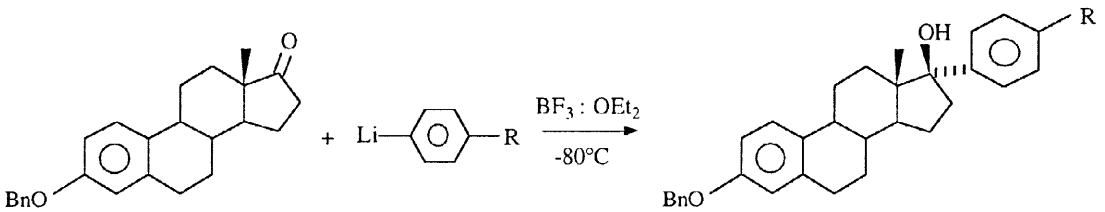
entry 1 : ArLi was prepared by Br/Li exchange in THF. EBE mixed with activation reagent (1.3 $LiClO_4$ / EBE) was added in the same solvent.
entry 2 : ArLi was prepared by Br/Li exchange in THF. BF_3 : OEt_2 (5.7/EBE) and then EBE in THF were added.
entry 3 : commercially available PhLi was dissolved in THF. EBE in THF and then BF_3 : OEt_2 (2.7/EBE) were added.
entry 4 : anhydrous $CeCl_3$ (2/EBE) was stirred for a night in THF at rt. PhLi was then added at -80°C and stirred for 0.5 h. EBE in THF was added at least.
entry 5 : $TiCl_4$ (2/EBE) was added to ether at -80°C, followed by PhLi [18]. EBE was then added in THF at -40°C.

Poor results are obtained by activation with metal halides (entries 4,5), the best activation method being the promoted addition with boron trifluoride etherate. Further experiments were then performed, in various solvents or with excess reagents, in order to optimize BF_3 promoted addition of PhLi to EBE. Table 2 summarizes the results.
The condensation of PhLi appeared to be achieved after 0.5h at -85°C (entry 1, table 2). No improvement was observed in THF with excess of PhLi and/or BF_3 : OEt_2 (entries 2,3).
80% EBE was converted into 17α-phenylestradiol by use of toluene as solvent (entry 5).
The BF_3 : OEt_2 promoted addition to EBE was then applied to other aryllithiums, including **3** (Fig. 2).

Table 2. n PhLi + EBE $\xrightarrow[-85°C]{n'BF_3:OEt_2}$ **4**

entry	n	n'	solvent	t(h)	% **4**
1	2.7	2.7	THF	0.5 to 1.5	56-60
2	4	4	THF	2	60
3	2.7	4	"	0.5	"
4	"	2.7	CH_2Cl_2	"	48
5	"	"	toluene	"	80

entries 1-3 : see table 1, entry 3.
entries 4,5 : EBE was dissolved in the solvent, then PhLi and $BF_3 : OEt_2$ were added.



2 R = Me, OMe, N-protected **4**

Fig. 2

The preparation of N-protected 4-aminophenyllithium, **3**, in THF has been previously described. 4-tolyllithium was better prepared, in ether at room temperature, by reaction of 4-bromotoluene with lithium[19]. This method did not work for preparation of p.anisyllithium, which was better obtained by I/Li exchange (4-iodoanisole in ether at -65°C + 1.25 BuLi for 2h).

Table 3 summarizes some of the results obtained for the reaction of different aryllithiums with EBE, with or without activation by $BF_3 : OEt_2$. No condensation occurred at low temperature without activation.

Table 3. n ArLi + EBE $\xrightarrow{n' BF_3: OEt_2}$ **4**

entry	Ar	n	n'	solvent	T°C	t (h)	% **4**
1	tolyl	3	0	toluene	20	24	55
2	"	"	3	mixed	-80	2	80
3	anisyl	2	0	toluene	20	67	60
4	"	3	4	mixed	-85	0.5	77
5	**3**	2.6	5.7	THF	-85	2	60

entry 1 : tolylLi was prepared by I/Li exchange in toluene (1 BuIi, 3h). EBE was then added in toluene.
entry 2 : ArLi was prepared in ether, according to (14). EBE was then added in toluene, followed by $BF_3 : OEt_2$.
entry 3 : ArLi was prepared by Br/Li exchange in toluene (1 BuLi, 3h). EBE was then added in toluene.
entry 4 : ArLi was prepared by I/Li exchange in ether at -65°C (1.25 BuLi, 2h). EBE was then added in toluene, followed by $BF_3 : OEt_2$.
entry 5 : ArLi, 3, was prepared in THF as previously described. $BF_3 : OEt_2$ was then added followed by EBE.

For tolyl and anisyllithium addition to EBE, reasonable percentages of conversion were observed, at room temperature after 1 to 3 days, withouth activation (entries 1, 3). The results were significantly improved by promoted BF_3 : OEt_2 addition of the same aryllithiums, at low temperature and with short reaction times (entries 2,4).
For N-protected aryllithium, **3**, poor conversion was observed by using an ether -toluene mixed medium ; the best result was obtained in THF (entry 5).
As an example, the synthesis of an estradiol **4** (R = Me) has been achieved following the conditions described in table 3, entry 2. Starting from 1.4 g EBE, 0.97 g of estradiol were obtained by cristallisation of the rough product in ether (53 % yield, F = 179°C).
This product presents a typical νOH at 3548 cm^{-1}, the NMR ^1H spectrum being in accordance with the structure : δ ppm in $CDCl_3$ = 1.08 (s, CH_3-18) ; 2.36 (s, 4-Me) ; 5.0 (s, CH_2-Ph) ; 6.7 (d, H-4) ; 6.72 (dd, H-2) ; 7.08 (d, H-1) ; 7.4 (m, H arom.).
The use of boron trifluoride etherate as a promoter favors the addition of selected aryllithiums on estrone and allows the easy and rapid formation of various 17α arylestradiols derivatives in satisfactory yields.

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