Pergamon

Tetrahedron Letters 42 (2001) 5409–5411

TETRAHEDRON LETTERS

Addition of aryllithiums to an 11-oxo-steroid

Vincent Lecomte, Nicolas Foy, Franck Le Bideau, Elie Stéphan* and Gérard Jaouen

Laboratoire de chimie organométallique, Ecole Nationale Supérieure de Chimie et CNRS, 11 rue Pierre et Marie Curie, 75005 Paris, France

Received 2 May 2001; accepted 12 June 2001

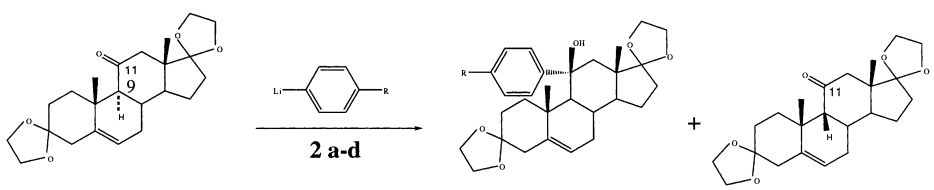
Abstract—The addition of aryllithiums to an 11-oxo-steroid is possible in non-polar medium and at room temperature. A series of protected 11α-aryl-11β-hydroxy-androsten-diones have been prepared.

Steroids substituted at position 11 by aryl groups are very much in demand for their biological properties, and their synthesis continues to attract considerable interest[1–5] particularly in an industrial context.[6] Access to derivatives of this type via organometallic additions onto 11-oxo-steroids has always remained problematic. In fact, 11-oxo-steroids possessing two angular methyl groups (pregnane or pregnene series, androstane or androstene, cortisone etc.) are fairly unreactive towards organometallic derivatives. The literature reports little more than the addition of methyllithium or methylmagnesium halides to steroids of this type,[7] as well as, more marginally, ethynylation[8] or allylation[9] reactions. Fonken[10] on the other hand has noted the lack of reactivity of phenyllithium and 4-methoxyphenyllithium towards a protected pregnan-11-one. Arylations in position 11 have therefore been performed via other routes. For example, Cleve[5] recently described the synthesis of 11-arylated compounds in the androstene series via a Suzuki coupling.

Here we describe the addition of a series of aryllithiums (**2a–d**) to an 11-oxo-steroid in the androstene series. Adducts **3** can be obtained in yields between 30 and 60% in non-polar media and at room temperature. The aryllithium addition reaction was performed on **1**, the diketal of adrenosterone[11] (Scheme 1).

The reaction was initially studied for the addition of phenyllithium **2a** onto the keto-steroid **1** in order to establish the most favorable parameters for this addition. The addition reaction may of course occur in competition with the classical enolization reaction, which after hydrolysis can lead to an epimerization of the steroid **1** in position 9 giving the product **4**.

Table 1 shows the results obtained by the reaction of phenyllithium with the steroid **1** under varying conditions of solvent, temperature and reaction time. The influence of lithium salt, present in commercial phenyllithium at a level of around 3%, was also tested by starting from a phenyllithium prepared by halogen/metal exchange,[12] and then used as such (entry 7) or with the addition of LiBr (entry 8).



1 **3 a-d** **4**

R = H, **a**; Me, **b**; OMe, **c**; NMe_2, **d**

Scheme 1.

Keywords: arylation; lithium compounds; 11-oxo-steroids.

* Corresponding author. E-mail: stephan@ext.jussieu.fr

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01033-4

Table 1. Reaction of steroid **1** with phenyllithium[a]

Entry	Solvent[b]	Temperature (°C)	Time (h)	% **1**	% **3a**	% **4**
1	THF	20	2	100	0	0
2	Toluene	20	2	50	50	0
3	Toluene	20	24	46	54	0
4	Toluene	60	24	30	30	40
5	Et_2O/toluene (60/40)	20	2	34	42	24
6	Et_2O/toluene (60/40) + TMEDA[c]	20	2	100	0	0
7[d]	Et_2O/toluene (45/55)	20	2	47	43	10
8[d]	Et_2O/toluene (45/55)	20	2	23	46	31

[a] The reaction is conducted with 3 equivalents of phenyllithium/steroid **1**. Commercial phenyllithium was used in experiments 1–6. In all cases, phenyllithium was added to a steroid solution.
[b] The reaction medium also contained approximately 10% saturated hydrocarbons. These are either cyclohexane when commercial phenyllithium is used (entries 1–6), or hexanes when phenyllithium is prepared by exchange starting from commercial BuLi (entries 7 and 8).
[c] Experiment conducted in the presence of TMEDA in 1/1 PhLi/TMEDA.
[d] Experiments 7 and 8 were carried out using phenyllithium prepared by reaction of bromobenzene with butyllithium at room temperature in ether. Experiment 7 was done without addition of LiBr, experiment 8 with 3 equivalents of LiBr/steroid **1**.

The percentage of the addition product **3a** is determined from the ^{1}H NMR spectrum of the crude reaction product recorded in $CDCl_3$, taking into consideration the integration of the angular methyl signals. These signals are strongly deshielded for the adduct (CH_3-18: signal at 0.82 ppm for **1**, 1.19 ppm for **3a**; CH_3-19: signal at 1.22 ppm for **1**, 1.34 ppm for **3a**) and thus indicate an 11β configuration for the OH group. Besides this well-known effect of deshielding of angular methyls by an OH in 11β[13] there is also a contribution from the aryl group in 11α, which may be estimated at +0.1 ppm for each of the two signals. The 9β epimer, **4**, was characterized by ^{1}H and ^{13}C NMR in $CDCl_3$. The formation of the epimer is signaled by the appearance in ^{1}H NMR of two further angular methyls (0.82 and 1.29 ppm) and a doublet corresponding to protons in C-7 or C-12 according to a ^{1}H–^{13}C shift-correlation (3.2 ppm).

The addition reaction does not occur in THF (entry 1). It does however take place in toluene or toluene–ether medium at room temperature (entries 2, 3, 5, 7 and 8) with the adduct **3** obtained in 42–54% yield. The presence of ether in the medium leads to increased competition from the enolization reaction at room temperature, as can be seen from the percentages found for the epimer **4** (entries 5, 7 and 8), without any increase in the rate of addition. Enolization does not take place after 2 h of reaction in toluene, according to an exploratory experiment with silylated enol ether, in agreement with the lack of formation of **4**. Prolonged heating in this solvent (entry 4) leads to a lower rate of addition and increased enolization. In this case the presence of lithium salt in the medium affects the addition rate only slightly, but does increase the epimerization rate (especially in entry 8).

The structure of phenyllithium in solution has been studied by Jackman[14] and Bauer.[15] This lithium compound exists in the form of a dimer in equilibrium with its monomer in THF, and in the form of a tetramer in toluene or hydrocarbon–ether. The mechanisms of addition of lithium compounds onto ketones also vary according to the medium.[16] In ether media, the kinetics causes dissociation of the dimer followed by addition of the monomer onto the ketone, while in a hydrocarbon medium a complex between the polymer and the ketone appears to form first, and the addition product is formed from this complex.

The addition reaction in THF of a phenyllithium monomer onto the hindered ketosteroid **1** would therefore not occur. However, it would seem that the formation of a tetramer–ketosteroid complex, followed by conversion to an adduct **3** is possible. When the lithium tetramer monomerizes on addition of a chelating ligand (Table 1, entry 6) there is logically no reaction.

Table 2. 11α-Aryl-11β-hydroxy-steroids **3a–d**

R	Yields[a] (%)	Mp (°C)	^{1}H NMR: δ (ppm)[b]		
			CH3-18	CH3-19	H aromatics
H (**3a**)	43	182	1.19	1.34	7.18–7.47 (m)
Me (**3b**)	40	171	1.19	1.34	7.08 (d); 7.31[c]
MeO (**3c**)	20	153	1.18	1.33	6.81 (d); 7.33[c]
NMe_2 (**3d**)[d]	25	–	1.22	1.48	7.58; 7.88

[a] As an isolated product.
[b] In $CDCl_3$ for **3a–c** and in CD_3OD for **3d**.
[c] Broad signal.
[d] In this case the steroid deprotected at positions 3 and 17 is obtained as the chlorhydrate.

The highest reactivity of tetrameric lithiums had already been observed in alkyllithium additions to ethylene in pentane.[17] The solvent effect observed here can also be compared to the work of Canonne[18] on addition of organomagnesium reagents to hindered ketones, in which it was possible to increase the rate of addition by using hydrocarbon diluents, to the detriment of the secondary reduction reaction. To explain the observed results, the author postulates a coordination effect of the Grignard reagent on the alkoxide thus formed.

A series of steroids **3** was then prepared by the addition of 3 equivalents of aryllithium to the steroid **1** under optimal conditions as previously established. Tolyllithium and 4-(*N*,*N*-dimethyl) phenyllithium were prepared by reaction of the brominated derivatives with lithium in ether.[19] Anisyllithium was prepared by an exchange reaction between 4-iodo-anisole and butyllithium in ether. The extent of addition of the aryllithiums (as established by ^{1}H NMR) varies between 31 and 60%. Table 2 shows the yields obtained after purification as well as some of the characteristics of the adducts. Elemental analysis of the latter is in agreement with the proposed structure.

Commercial phenyllithium and anisyllithium prepared by exchange were added to a solution of the steroid **1** in toluene, while the steroid in toluene solution was added to the lithiums **2b** and **2d**. The medium was hydrolyzed after 5–17 h at room temperature. After extraction by dichloromethane and the usual work-up, the steroids **3a–c** were separated from the starting material by chromatography on a silica column with a mixture of AcOEt/petroleum ether (4/6) as eluent. This purification method was not possible for the addition product **3d**, which shows the same R_F as the starting steroid. The addition product must therefore be obtained in two steps: crystallization of steroids **1** and **3d** in cyclohexane, followed by filtration (to eliminate *N*,*N*-dimethylaniline and eventually 4-bromo-*N*,*N*-dimethylaniline, which has not been transmetalated-formed during hydrolysis) then treatment of a solution of the steroid mixture in THF by dilute HCl to obtain the chlorhydrate of **3d**. The two ketone functions are deprotected by this acid treatment.

In conclusion, the addition of aryllithiums to a protected adrenosterone allowed synthesis of a series of protected 11α-aryl-11β-hydroxy-androsten-diones in overall acceptable yields, considering the low reactivity of 11-oxo-steroids. These steroids should allow access to 11-arylated testosterones in three steps: a deoxygenation step at position 11, currently under study, a deprotection and a selective reduction in position 17. We are of course hoping to find an 11β stereochemistry for aryl groups, specifically to obtain a short route from commercial adrenosterone to an analog of mifepristone[20] (RU 486), the first known progesterone antagonist.

Acknowledgements

We wish to thank B. McGlinchey for her assistance in translating the manuscript.

References

1. Geisler, J.; Cleve, A.; Harre, M. *Tetrahedron* **2000**, *56*, 6489–6492.
2. Rao, P. N.; Acosta, C. K.; Bahr, M. L.; Burdett, J. E.; Cessac, J. W.; Morrison, P. A.; Kim, H. K. *Steroids* **2000**, *65*, 395–400.
3. Hazra, B. G.; Basu, S.; Pore, V. S.; Joshi, P. L.; Pal, D.; Chakrabarti, P. *Steroids* **2000**, *65*, 157–162.
4. Rao, P. N.; Wang, Z.; Cessac, J. W.; Rosenberg, R. S.; Jenkins, D. J. A.; Diamandis, E. P. *Steroids* **1998**, *63*, 523–530.
5. Cleve, A.; Fritzemeier, K. H.; Heinrich, N.; Klar, U.; Müller-Fahrnow, A.; Neef, G.; Ottow, E.; Schwede, W. *Tetrahedron* **1996**, *52*, 1529–1542.
6. As shown by the number of patents cited in Chemical Abstracts.
7. Kirk, D. N.; Petrow, V. *J. Chem. Soc.* **1961**, 2091–2098 and references cited therein.
8. Shoppee, C. W.; Lack, R. E. *J. Chem. Soc.* **1962**, 3624–3629.
9. Wieland, P.; Kalvoda, J. *Tetrahedron Lett.* **1983**, *24*, 5603–5606.
10. Fonken, G. S. *J. Org. Chem.* **1965**, *30*, 2095–2096.
11. Bernstein, S.; Littell, R.; Williams, J. H. *J. Am. Chem. Soc.* **1953**, *75*, 1481–1482.
12. Gilman, H.; Langham, W.; Moore, F. W. *J. Am. Chem. Soc.* **1940**, *62*, 2327–2335.
13. Bridgeman, J. E.; Cherry, P. C.; Clegg, A. S.; Evans, J. M.; Jones, E. R. H.; Kasal, A.; Kumar, V.; Meakins, G. D.; Morisawa, Y.; Richards, E. E.; Woodgate, P. D. *J. Chem. Soc. (C)* **1970**, 250–257.
14. Jackman, L. M.; Scarmoutzos, L. M. *J. Am. Chem. Soc.* **1984**, *106*, 4627–4629.
15. Bauer, W.; Winchester, W. R.; Schleyer, P. von R. *Organometallics* **1987**, *6*, 2371–2379.
16. Al-Aseer, M. A.; Smith, S. G. *J. Org. Chem.* **1984**, *49*, 2608–2613.
17. Kammermeier, B. O. T.; Klumpp, G. W.; Kolthof, K.; Vos, M. *Tetrahedron Lett.* **1991**, *32*, 3111–3114.
18. Canonne, P.; Foscolos, G.; Caron, H.; Lemay, G. *Tetrahedron* **1982**, *38*, 3563–3568.
19. Gilman, H.; Zoellner, E. A.; Selby, W. M. *J. Am. Chem. Soc.* **1933**, *55*, 1252–1257.
20. Teutsch, G.; Philibert, D. *Hum. Reprod.* **1994**, *9* (Suppl. 1), 12–31.