Pergamon

Tetrahedron Letters 40 (1999) 7095–7098

TETRAHEDRON LETTERS

Organolithium mediated synthesis of prenylchalcones as potential inhibitors of chemoresistance

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Received 15 June 1999; accepted 28 July 1999

Abstract

A number of substituted chalcones have been prepared by a novel LiHMDS-mediated aldol condensation, the first method consistent with the use of alkali-labile protecting groups such as *tert*-butyldiphenylsilyl or *tert*-butyldimethylsilyl. Chalcone substitution by prenylation increases their binding affinity to P-glycoprotein responsible for cancer cells chemoresistance.

Keywords: aldol reaction; biologically active compounds; chalcones; protecting groups.

We have recently demonstrated that flavonoid compounds behave as bifunctional modulators of P-gp (transporter involved in the chemoresistance of cancer cells) which interact both with the ATP-binding site and a hydrophobic steroid-binding site.[1] Flavonoids occasionally exist in plants as *C*-prenylated derivatives.[2] The latter display a strong lipophilic character and are therefore expected to better interact with the steroid-binding site of P-gp. To study the effects of *C*-prenylation on the binding to P-gp, chalcones are good candidates because their preparation is easier than that of other classes of flavonoid compounds. However, the synthesis of chalcones by usual aldol condensations in boiling hydroalcoholic potassium hydroxide sometimes suffers severe limitations. For example, in the preparation of prenylchalcones, protection of the phenolic hydroxyls by a MEM group is required;[3] however, the acidic removal of the MEM protecting group may result in the cyclization of the prenyl chain with the neighboring phenolic hydroxyls. In addition, a more easily cleaved protecting group such as *tert*-butyldiphenylsilyl (TBDPS)[4] is not stable under the conditions of classical aldol condensation. On the other hand, the use of organolithium reagents such as lithium-bis(trimethylsilyl)amide[5] (LiHMDS) or lithium diisopropylamide[6,7] has been reported in aldol-type reactions.

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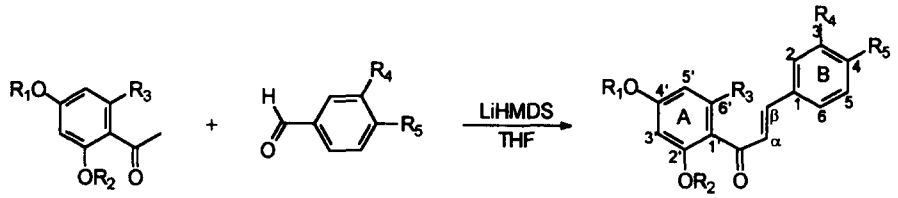
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01461-6

In the present paper, we report the first use of LiHMDS-mediated aldol condensation in the preparation of prenylchalcones. This method, coupled with the use of the easily removable *tert*-butyldiphenylsilyl or *tert*-butyldimethylsilyl groups, gave better results than the other usual protecting groups like MEM or THP.

Acetophenones (**1a–d**) in solution in dry THF were metalated with LiHMDS and reacted with aldehydes (**2a–f**) at different temperature (Scheme 1). The yields in chalcones (**3a–h**) are given in Table 1.



1

a : R_1=R_2=R_3=H
b : R_1=R_2=H; R_3=OH
c : R_1=TBDPS; R_2=R_3=H
d : R_1=R_2=Bn; R_3=H

2

a : R_4=H; R_5=OH
b : R_4=R_5=OH
c : R_4=H; R_5=TBDPSO
d : R_4=R_5=H
e : R_4=Pr; R_5=TBDPSO
f : R_4=Pr; R_5=TBDMSO

3

a : R_1=R_2=R_3=R_4=H; R_5=OH
b : R_1=R_2=R_3=H; R_4=R_5=OH
c : R_1=R_2=H; R_3=R_4=R_5=OH
d : R_1=TBDPS; R_2=R_3=R_4=H; R_5=TBDPSO
e : R_1=R_2=Bn; R_3=R_4=R_5=H
f : R_1=TBDPS; R_2=R_3=R_4=R_5=H
g : R_1= TBDPS; R_2=R_3=H; R_4=Pr; R_5=TBDPSO
h : R_1=TBDPS; R_2=R_3=H; R_4=Pr; R_5=TBDMSO

Scheme 1.

We first attempted to directly obtain hydroxychalcones from their corresponding unprotected precursors. The yields decreased with an increasing number of phenolic hydroxyls (Table 1, entries 1–3). However yields were greatly improved when protecting groups such as TBDPS (Table 1, entries 4 and 8) or Bn (Table 1, entry 5) were used. In fact; when the reaction was performed at –78°C, LiHMDS condensation of dibenzyl resacetophenone **1d** with benzaldehyde **2d** gave the same yield in chalcone **3e** (40%, Table 1, entry 5) as when classical alcoholic potassium hydroxide conditions were used (result not shown). Furthermore, the yields in benzylchalcone **3e** increased with increasing condensation temperature (Table 1, entries 5–7). The maximum yield in **3e** (48%) was obtained using refluxing conditions. We obtained similar results with TBDPS protecting group which was found to be stable under these reaction conditions (Table 1, entries 8–10), yielding **3f** in 50% maximum yield.

Table 1
Aldol condensation of acetophenones and aldehydes using the LiHMDS method

N°	Acetophenone	Aldehyde	Chalcone	Conditions °C, h	Yield %
1	**1a**	**2a**	**3a**	-78°C, 12h	15
2	"	**2b**	**3b**	"	8
3	**1b**	"	**3c**	"	0
4	**1c**	**2c**	**3d**	"	33
5	**1d**	**2d**	**3e**	"	40
6	"	"	"	20°C, 12h	40
7	"	"	"	reflux, 1h	48
8	**1c**	"	**3f**	-78°C, 12h	34
9	"	"	"	20°C, 12h	39
10	"	"	"	reflux, 1h	50
11	"	**2e**	**3g**	-78°C, 12h	4
12	"	**2f**	**3h**	reflux, 1h	25

Table 2
Comparison of three methods in the preparation of 3-prenyl-2′,4′,4-trihydroxychalcone[10]

	Resacetophenone protection (**a**)	4-Hydroxy-3-prenylbenz--aldehyde protection (**b**)	Aldol condensation (**c**)	Corresponding chalcone deprotection (**d**)	Overall yield
TBDMS/TBDPS (**I**)	99	96	25	100	24
MEM (**II**)	94	59	12	17	1.2
THP (**III**)	41	77	17	95	6.6

Ia: TBDPS-Cl/imidazole/DMF; **Ib**: TBDMS-Cl/imidazole/DMF; **Ic**: LiHMDS/dry THF/reflux; **Id**: tetrabutylamonium fluoride/THF
IIa-IIb: MEM-Cl/*N,N*-diisopropylethylamine/DMF; **IIc**: aq. KOH/MeOH/reflux; **IId**: HCl/MeOH/reflux
IIIa-IIIb: 3,4-dihydro-2*H*-pyrane/pyridinium *p*-toluenesulfonate/CH_2Cl_2; **IIIc**: aq. KOH/MeOH/reflux; **IIId**: HCl/EtOH

The synthesis of prenylchalcones is usually considered as being difficult. Special conditions are required for aldol condensation, such as reaction in ethanolic KOH at room temperature,[8] or in refluxing methanolic potassium trimethylsilanolate.[3,8] The synthesis of B-ring prenylated chalcones appears even more difficult. Actually, under the above mentioned conditions, the reaction of protected prenylacetophenone with prenylaldehyde, leads to the corresponding chalcone in 8.8% yield only.[9] Therefore the LiHMDS condensation was then tested in the preparation of B-ring prenylchalcones. Reaction of TBDPS-resacetophenone **1c** with prenylaldehyde **2e** at −78°C gave chalcone **3g**, in 4% yield, only (Table 1, entry 11). The best yield (25%) was obtained, as expected, when TBDPS-resacetophenone **1c** was condensed with TBDMS-prenylaldehyde **2f** under refluxing conditions† (Table 1, entry 12).

Finally, the novel LiHMDS method was compared with the usual method for prenylchalcone synthesis, using either MEM, or THP as protecting groups (Table 2).

Concerning the aldol condensation step, the LiHMDS method gave the best results. Of the three methods, the one using MEM as protecting group was by far the less advantageous, due to the very poor deprotection yield (17%). On the contrary, both THP and TBDMS/TBDPS groups were removed in excellent yield (95 and 100%, respectively). However protection of the acetophenone and aldehyde precursors was much more efficient using TBDMS/TBDPS groups rather than using the THP group. Therefore the LiHMDS method can undoubtedly be considered more advantageous, because it is the only one allowing the use of silicium-based protecting groups.

3-Prenyl-2′,4′,4-trihydroxychalcone,[10] here prepared in improved yield, binds to P-gp with a 20-fold higher affinity as compared with the non-prenylated chalcone (K_D of 0.53 μM instead of 11.6 μM, when measured by the assay procedure described previously[1]).

In conclusion, LiHMDS is a useful reagent for the preparation of prenylchalcones as potential high affinity inhibitors of chemoresistance. When protected acetophenone and aldehyde precursors are used, the yields of the LiHMDS method are higher than for classical methods using methanolic potassium hydroxide whatever the protecting group used. On the other hand, LiHMDS condensation allows the use of an alkali-labile protecting group like TBDPS. The latter protecting group will certainly offer in the future interesting perspectives in the synthesis of prenylchalcones, since it can be easily removed under non-degrading conditions for the prenyl chain.

† Typical procedure: To a mixture of 4′-TBDPS-resacetophenone **1c** (1 equiv.) and 3-prenyl-4-TBDMSilyloxybenzaldehyde **2f** (1 equiv.) in solution in dry THF were added 3 equiv. of LiHMDS (1 M solution in dry THF) under argon. The reaction medium was refluxed for 1 h, diluted with ice-cold HCl solution (0.4 M), stirred for an additional 15 min and extracted with ethyl acetate.

Acknowledgements

The authors are grateful to Université Claude Bernard, Région Rhône-Alpes and Ligue Contre le Cancer for financial support.

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