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Efficient coupling and solid-phase synthesis of steroidal ketone derivative using polymer-bound glycerol

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Abstract

High-yield coupling of steroidal hindered ketones onto polymer-bound glycerol by an efficient acetal exchange reaction is reported under mild conditions. A solid-phase model sequence of five steps is thereafter achieved to synthesize a steroidal ketone derivative having two levels of diversity in good yield and purity. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: solid-phase synthesis; acetals; steroids; ketones.

During continuing efforts to develop potent inhibitors of key steroidogenic enzymes and antagonists of steroid receptors,[1–5] we became interested in attaching a steroidal hindered ketone to a solid support as this linked steroid could be used as a precursor for the solid-phase synthesis of combinatorial libraries of steroid derivatives. The pioneering work of Leznoff has shown that the formation of an acid labile acetal linker between a carbonyl group and polymer-bound 1,2- or 1,3-diols was feasible. However, although this reaction worked well with aldehydes, the same was not true for ketones.[6–8] The classic acetalization reaction performed with a variety of diketones and diol resin **1**, with *p*-toluenesulfonic acid (*p*-TSA) as catalyst in refluxing benzene (azeotropic removal of water), produced only moderate coupling–decoupling yields (19–72%) (Scheme 1), even after a long reaction time (48 h) with an excess of diketone. Under the same acetalization conditions and replacing ether resin **1** with the thioether resin **2**, Hodge and Waterhouse[9] reported the low coupling–decoupling yields of 5 and 30%, for steroidal ketones 3β-acetoxy-5α-androstane-17-one and 5α-cholestan-3-one, respectively.

Another approach using a ketimine linker to link ketones with good coupling–decoupling yield has also been described.[10,11] However, the ketimine function is known to react with many reagents which often precludes its use in combinatorial chemistry. To date, there are no simple methods for using a chemically stable linker, under mild conditions, in the direct and efficient coupling of steroidal ketones to the solid phase. In our view, Leznoff's linker still showed promise for implementation in various combinatorial

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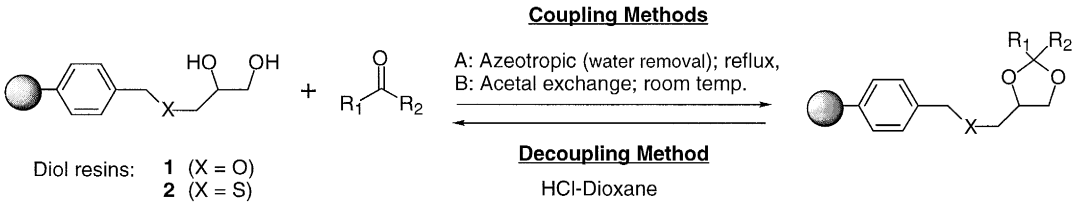
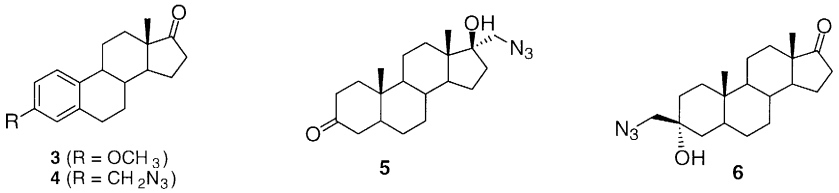


Scheme 1. Coupling and decoupling reactions of aldehydes and ketones onto diol resin **1** or **2**

routes, especially when considering the chemical versatility of the acetal function and the stability of the ether (X = O) link. In this report, novel acetalization conditions were investigated using diol resin **1** to optimize the coupling–decoupling yields of hindered steroidal ketones **3**–**6**. Furthermore, a model sequence of reactions with steroid precursor **6** was described to show the usefulness of the acetal linker for the further elaboration of steroidal ketone libraries.



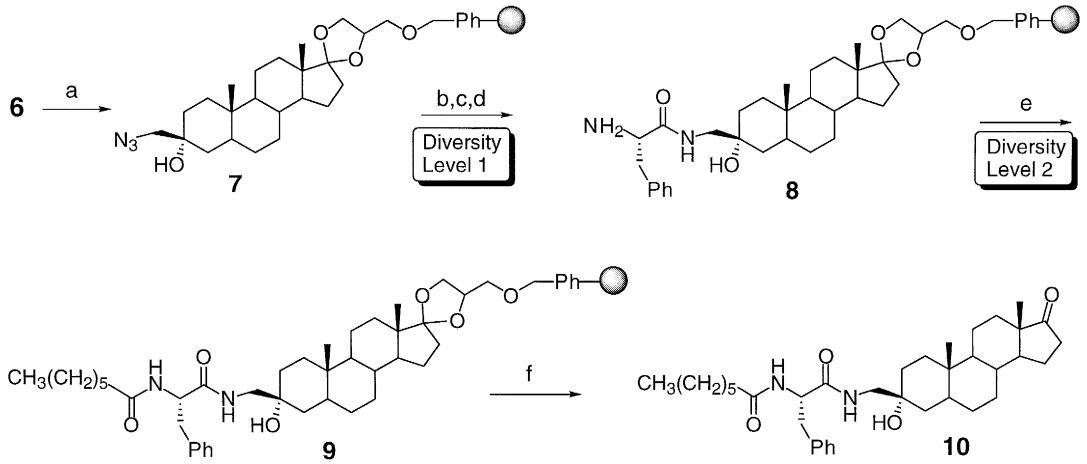
The coupling assays were first performed with an azeotropic method (A) by varying the solvent, the reaction time, and concentration of the catalyst. In the best case, the yields obtained for the coupling of methyl-*O*-estrone (**3**) with diol resin **1** did not exceed 25% (Table 1, entry 1) and the decoupled product showed signs of high-heat resin decomposition (15%). The azeotropic coupling method was therefore not considered suitable for this type of assay, due to the high ketone concentration and long reaction time

Table 1
Comparative results for acetalization of diol resin **1** and steroidal ketones **3**–**6** using method A (azeotropic) or method B (acetal exchange)

Entry	Ketone	eq[a]	Coupling Method[b]	Catalyst [% mol]	Time (h)	Yield (%)[c]
1	**3**	5.0	A	*p*-TSA [50]	48	25
2	**3**	1.2	B	*p*-TSA [10]	4	25
3	**3**	1.2	B	*p*-TSA [10]	16	72
4	**3**	3.0	B	*p*-TSA [10]	4	59
5	**3**	5.0	B	*p*-TSA [10]	4	51
6	**3**	1.2	B	$Sc(OTf)_3$ [5]	4	77
7	**3**	1.2	B	$Sc(OTf)_3$ [5]	16	79
8	**3**	3.0	B	$Sc(OTf)_3$ [5]	16	88
9	**3**	5.0	B	$Sc(OTf)_3$ [5]	4	99
10	**4**	3.0	B	$Sc(OTf)_3$ [5]	16	84
11	**5**	3.0	B	$Sc(OTf)_3$ [5]	16	89
12	**6**	3.0	B	$Sc(OTf)_3$ [5]	16	83

a) Equivalent of ketone according to the loading (1.0 mmol/g) of polymer-bound glycerol (**1**); b) Azeotropic removal of water in refluxing toluene (A) or acetal exchange reaction using TMOF in toluene at rt (B); c) For coupling-decoupling reactions

required at high temperature (110°C). We then turned our attention to an alternative method (B), which was based on an in-solution acetal exchange reaction previously reported to give excellent yields at room temperature. The ketone, in the presence of trimethylorthoformate (TMOF) and acid catalyst, yielded a dimethoxy acetal intermediate that participated, in situ, in an acetal exchange reaction with the diol to give the desired cyclic acetal and methanol.[12,13] A variant of this reaction using triethylorthoformate and *p*-TSA with sodium sulfate in refluxing benzene (48 h) was used by Leznoff, but the coupling yields (45–65%) were not better than method A for various diketones. We investigated the acetal exchange reaction on solid phase (entries 2–9) based on the reaction conditions developed in solution by Ishihara.[14] Because the desired ketone often required many synthetic steps before its coupling to a solid support, we became concerned by the large quantity of ketone substrate used in the coupling step. We first tried coupling with only 1.2 equiv. of ketone and optimized the conditions by using scandium triflate (entries 6 and 7) instead of *p*-TSA (entries 2 and 3) as a catalyst. Alternatively, an excess of ketone (3.0 equiv. or 5.0 equiv.) gave almost quantitative yields (88 and 99%) for coupling–decoupling reactions with $Sc(OTf)_3$ (entries 8 and 9), but lower yields (59 and 51%) were observed with *p*-TSA (entries 4 and 5). In both cases, the excess of ketone was easily recovered from the resin by simple filtration followed by flash chromatography. Similar to solution-phase experiments, in the solid phase, the use of $Sc(OTf)_3$ was more effective than *p*-TSA, which required more catalyst and a longer reaction time. Using the selected conditions of method B (entry 8), the three key steroid precursors **4**–**6** were successfully linked to diol resin **1** (entries 10–12).



Scheme 2. (a) Steroidal ketone **6** (0.75 mmol), diol resin **1** (0.25 mmol),[15] TMOF (0.75 mmol), $Sc(OTf)_3$, toluene, rt; (b) $SnCl_2$ (0.2 M), PhSH (0.8 M), Et_3N (1.0 M), THF, rt; (c) L-Phe-Fmoc (0.5 mmol), PyBOP (0.5 mmol), HOBt (0.5 mmol), DIPEA (1.0 mmol), DMF, rt; (d) piperidine:CH_2Cl_2 (2:8), rt; (e) heptanoic acid (0.75 mmol), PyBOP (0.75 mmol), HOBt (0.75 mmol), DIPEA (1.5 mmol), DMF, rt; (f) 2.0 N HCl in dioxane (containing 0.03% of H_2O), rt

After optimizing the coupling reaction of hindered steroidal ketones, we performed a model solid-phase synthesis using the steroidal ketone **6** as precursor to generate future combinatorial libraries (Scheme 2). The ketone **6** (259 mg) was then coupled onto the polymer-bound glycerol (diol resin **1**) (250 mg) under the same conditions as the entry 8. The presence of the acetal linkage (119.4 ppm) and the azide function (2098 cm^{-1}) was confirmed by ^{13}C gel phase NMR[16] and IR spectrum, respectively. The azide group of steroid-bound resin **7** was reduced for 4 h under argon, with a solution of tin(II) chloride, thiophenol, and triethylamine in dry THF,[17] to give the corresponding amine as seen by the complete disappearance of the azide band. To introduce the first level of diversity, the free amino group was treated with Fmoc-protected L-phenylalanine using PyBOP, HOBt and diisopropylethylamine (DIPEA) in dry

DMF and under argon for 1 h. The Fmoc protective group was then removed with a solution of piperidine (20%) in dichloromethane to provide the amino acid steroid-bound resin **8**. The treatment of the resin **8** with the mixed anhydride resulting from heptanoic acid, PyBOP, HOBt and DIPEA gave the resin **9**, which held a second level of diversity. The final release of steroidal ketone **10** from the resin **9** was performed using a solution of 2.0 N HCl in dioxane for 2 h at room temperature. After a basic work-up (10% $NaHCO_3$), and extraction with dichloromethane, the desired steroid **10** was obtained in good overall yield (70%) from **6** and high HPLC purity (94%). The androsterone derivative **10** was characterized by ^{1}H NMR, ^{13}C NMR, IR and MS analysis.[18]

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References

1. Ciobanu, L.; Boivin, R.; Luu-The, V.; Labrie, F.; Poirier, D. *J. Med. Chem.* **1999**, *42*, 2280–2286.
2. Tremblay, M. R.; Poirier, D. *J. Steroid Biochem. Molec. Biol.* **1998**, *66*, 179–191.
3. Maltais, R.; Poirier, D. *Tetrahedron Lett.* **1998**, *39*, 4151–4154.
4. Tremblay, M. R.; Poirier, D. *Tetrahedron Lett.* **1999**, *40*, 1277–1280.
5. Tremblay, M. R.; Simard, J.; Poirier, D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2827–2832.
6. Leznoff, C. C.; Wong, J. Y. *Can. J. Chem.* **1973**, *51*, 3756–3764.
7. Leznoff, C. C.; Greenberg, S. *Can. J. Chem.* **1976**, *54*, 3824–3829.
8. Xu, Z. H.; McArthur, C. R.; Leznoff, C. C. *Can. J. Chem.* **1983**, *61*, 1405–1409.
9. Hodge, P.; Waterhouse, J. *J. Chem. Soc. Perkin Trans. 1* **1983**, 2319–2323.
10. McArthur, C. R.; Worster, P. M.; Jiang, J. L.; Leznoff, C. C. *Can. J. Chem.* **1982**, *60*, 1836–1841.
11. Worster, P. M.; McArthur, C. R.; Leznoff, C. C. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 221–222.
12. Wohl, R. A. *Synthesis* **1974**, 38–40.
13. Wenkert, E.; Goodwin, T. E. *Synth. Commun.* **1977**, *7*, 409.
14. Ishihara, K.; Karumi, Y.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 839–841.
15. Polymer-bound glycerol (Aldrich; 47,541-6; Lot: 11830DS). Obtained from 1.0 mmol/g Merrifield resin.
16. Lorgé, F.; Wagner, A.; Mioskowski, C. *J. Comb. Chem.* **1999**, *1*, 25–27.
17. Bartra, M.; Romea, P.; Urpi, F.; Vilarasa, J. *Tetrahedron* **1990**, *46*, 587–594.
18. Spectroscopic data for **10**: IR ν (KBr): 3300 (NH and OH), 1741 (C=O), 1654 (NC=O) cm^{-1}; ^{1}H NMR δ ($CDCl_3$): 0.73 (s, 3H), 0.85 (s, 3H), 0.87 (t, *J*=6.4 Hz, 2H), 1.0 to 2.10 (28H), 2.15 (t, *J*=7.6 Hz, 2H), 2.40 (m, 3H), 3.08 (m, 4H), 3.64 (s, 1H), 4.67 (q, *J*=7.3 Hz, 1H), 6.20 (m, 2H), 7.23 (m, 5H) ppm; ^{13}C NMR δ ($CDCl_3$): 11.16, 13.73, 13.97, 20.17, 21.66, 22.41, 25.52, 28.07, 28.78, 29.60, 30.66, 30.74, 31.46, 33.23, 34.95, 35.73, 35.98, 36.41, 37.65, 38.42, 40.28, 47.70, 50.93, 51.40, 54.18, 54.63, 71.19, 126.84, 128.48 (2×), 129.25 (2×), 136.60, 171.91, 173.49, 221.29 ppm; LRMS: 579.6 *m/z* for $C_{36}H_{55}N_2O_4$ [MH^+].