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MONO AND SEQUENTIAL BIS SOLID PHASE ALKYLATIONS OF A (*R*)-PHENYLGLYCINOL DERIVED PYRROLIDINONE SCAFFOLD

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Abstract - The preparation of piperidine- and pyrrolidinone-like polymer supported (*R*)-phenylglycinol derived scaffolds is described. Alkylation reactions were performed as a model transformation of these templates on the solid support which highlight some specific limitations in the use of (*R*)-phenylglycinol on the resin. Whereas the polymer supported piperidine was completely void of reactivity, alkylation of the pyrrolidinone counterpart proceeded with good yield, purity and control of mono- over bis-alkylation but with low diastereomeric excess.

Substituted heterocyclic compounds which offer a high degree of structural and conformational diversity provide a major target in medicinal chemistry because of their potential in the drug discovery process. Whereas many heterocycles can be accessed by specifically biassed solid phase syntheses, the development of a general solid phase methodology for the construction of a wide diversity of compounds remains a challenging task.[1]

For many years we have developed a synthetic methodology enabling substitution at different positions of various multifunctional ring systems using (*R*)-phenylglycinol as a source of both nitrogen and chirality such as in compounds (**1**) and (**2**) (Figure).[2-4]

Thus far only few attempts of using chiral auxiliaries on the solid phase have been reported.[5] We are currently investigating the use of immobilized (*R*)-phenylglycinol or its enantiomer and in this

communication we wish to report some preliminary results in the preparation of polymer-supported (*R*)-phenylglycinol derived scaffolds which were submitted to alkylation reactions as a model transformation on the solid support.

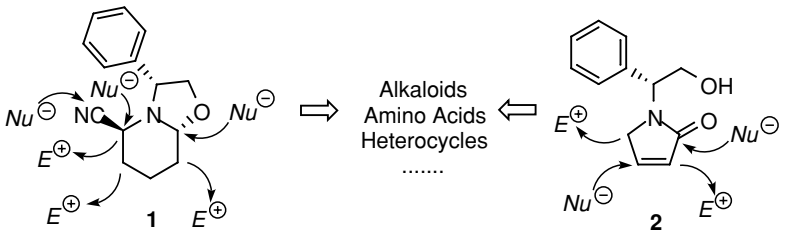
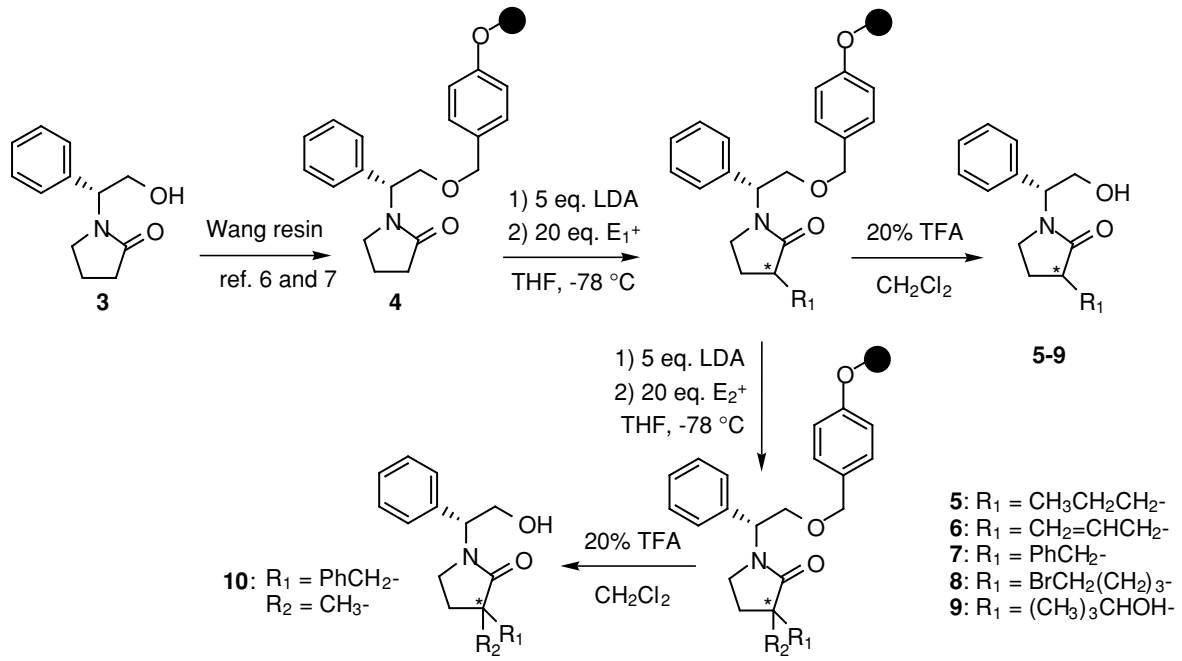


Figure : (*R*)-phenylglycinol derived scaffolds showing high combinatorial potential.

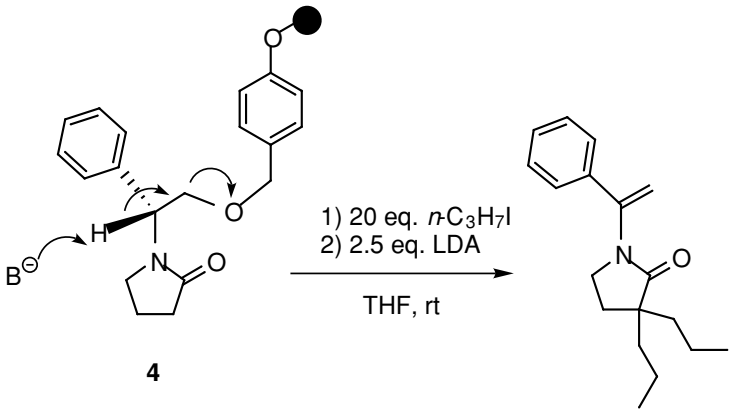
The range of templates developed in our laboratory either completely or partially integrates (*R*)-phenylglycinol. The hydroxyl group in compounds such as (**2**) is thus available for attachment to polymers, whereas compounds such as (**1**) may be linked to polymers through a phenolic hydroxy group using (*R*)-hydroxyphenylglycinol instead of (*R*)-phenylglycinol.



Scheme 1 : Preparation and alkylation of resin-supported pyrrolidinone (**4**)**.**

The preparation of a suitable resin-supported (*R*)-phenylglycinol derived pyrrolidine scaffold is shown in Scheme 1. Compound (**3**) was easily obtained from (*R*)-phenylglycinol as previously described by our

group[4] and subsequent loading of Wang resin (0.58 mmol/g) was accomplished through polymer activation with trichloroacetonitrile following a protocole as reported by Hanessian[6] and Eda.[7] The substitution-level of the resin was estimated through acidic cleavage and calculated to be 0.52 mmol/g (90%). In order to test the reactivity of the polymer-bound auxiliary (**4**) different alkylation conditions were examined. After some experimentation it was found of the utmost importance to conduct the alkylation reactions at –78 °C because room temperature addition of first the halogen derivative to the resin-supported scaffold and then the base, only gave undesired elimination products which were either mono- or bis-alkylated depending upon the excess of base used (Scheme 2).



Scheme 2 : Undesired elimination from the resin under room temperature alkylation conditions.

Deprotonation was therefore effected (Scheme 1) in THF at –78 °C with LDA (5 eq.) for 10 min followed by treatment with various electrophiles (20 eq.) for 20 min, the suspension was then collected on a glass filter and washed. The resin was either directly cleaved using 20% trifluoroacetic acid in CH_2Cl_2 or submitted to a second alkylation cycle with subsequent cleavage. The results are summarized in the Table. It is noteworthy that only monoalkylation (compounds (**5-9**)) occurred regardless of the excess of reagents (base and electrophiles) used. This allowed the sequential bis-alkylation leading to a chiral quaternary center next to the carbonyl-group in good yield but with moderate selectivity (compound (**10**)).

The diastereomeric excess was determined by HPLC analysis of the crude reaction mixture obtained after cleavage from the resin. The diastereomeric selectivities of the alkylation on the resin proved to be low as compared to classical « liquid phase » alkylation conditions of **3**, generally in the range of 80 - 90 %.[4] It should be noticed that no isomerization was observed under the acidic cleavage conditions for the optically pure derivatives obtained by solution phase chemistry.[4]

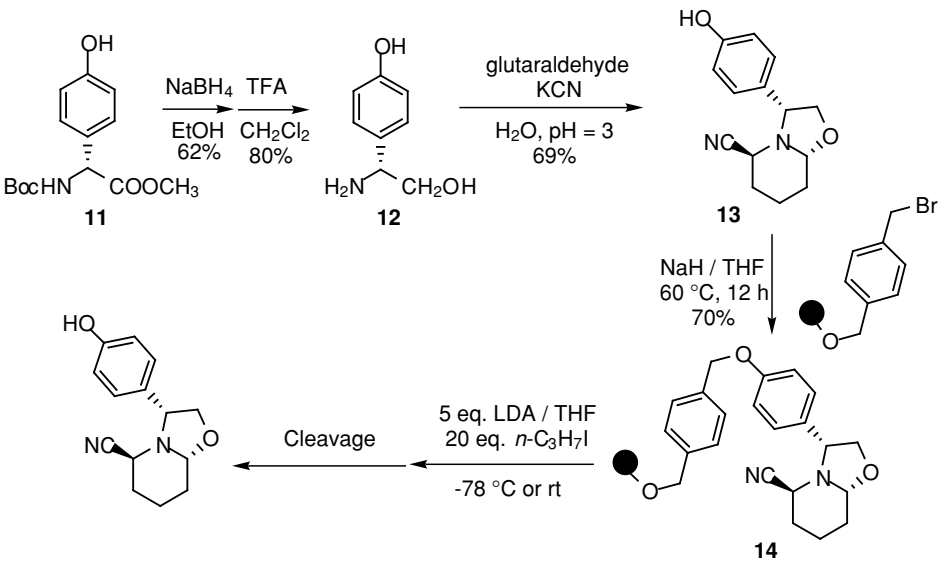
product[a]	electrophile (E_1^+/E_2^+)	yield (%)[b]	d.e. (%)[c]	configuration[d]
5	n-C_3H_7I	71	12	
6	CH_2=CH-CH_2Br	90	24	
7	$PhCH_2Br$	75	16	*R* (major) *S* (minor)
8	$Br(CH_2)_4Br$	78	22	
9	$(CH_3)_3CCHO$	92	-[e]	
10	$PhCH_2Br$ / CH_3I	72	46	

Table: Data concerning the alkylation of compound (**4**) with various electrophiles.

(a) All products were characterized by ^1H and ^{13}C NMR spectroscopy after separation of diastereomers by chromatographic means. (b) Isolated yield. (c) Determined by analytical HPLC on the crude cleavage mixture using a C8 Kromasil column with 0.05% TFA in H_2O and CH_3CN as eluent. (d) See text for details. (e) NMR analysis showed equimolar presence of diastereoisomers which proved unseparable by chromatographic means.

The configuration of the newly created asymmetric centre was assigned for both diastereomers of compound (**7**) by comparison of HPLC and NMR data with a reference compound of known *1'-R,3-S* configuration.[4] Interestingly, the *RS*-configuration was as such attributed to the minor isomer of compound (**7**) indicating a priviliged attack on the opposite site as compared to solution phase conditions.[4] Indeed, high diastereoselectivities in solution phase were explained by rigidifying the structure through chelation of lithium and induction of alkylation on the less hindered face, opposite the phenyl group. Such chelation might be difficult on the resin due to the bulk and proximity (site attachment) of the polymer. As d.e. on the resin was rather low we decided to enhance the steric hindrance by attaching the auxiliary (**3**) to a trityl resin[8] and tempting alkylation at –78 °C or at room temperature. All efforts to alkylate were unsuccessful as we recovered only starting material after cleavage from the resin. Interestingly, no elimination was observed at room temperature, illustrating the importance of the bulk of the trityl-polymer as compared to the Wang resin.

The preparation of the resin supported (*R*)-4-hydroxy phenylglycinol derived oxazolopiperidine auxiliary (**14**) is depicted in Scheme 3. Compound (**12**) was first obtained from conveniently protected (*R*)-hydroxyphenylglycine followed by reduction of the ester group using sodium borohydride in ethanol and removal of the Boc-group. The resulting alcohol was subsequently condensed with glutaraldehyde and KCN following a procedure as reported by our group[9] yielding a major crystalline product (**13**)[10] which configuration was assumed to correspond with its non-hydroxylated analogue (**1**) (Figure).[2]



Scheme 3 : Preparation of (*R*)-4-hydroxyphenylglycinol derived oxazolopiperidine scaffold (**14**).

Compound (**13**) was conveniently linked to the polymer through nucleophilic displacement of bromo-derived Wang resin[11] in 70 % yield. Unfortunately all attempts of alkylation were unsuccessful and resulted only in recovery of the starting material after cleavage from the resin. This complete lack of reactivity might be explained as compared to the pyrrolidinone analogue by a marked difference in accessibility of the reaction site when attached to the resin. Indeed, when associated to the bulk of the polymer backbone the oxazolopiperidine auxiliary with its rigid bicyclic structure can present a strongly reduced mobility and limit accessibility for deprotonation and alkylation. The pyrrolidinone analogue is clearly more flexible as protons are accessible for deprotonation as shown by the preparation of compounds (**5-10**) (Table).

In summary, we have demonstrated that not only the bulk and site attachment of the resin but also the rigidity of the scaffold strongly influences reactivity of the polymer supported structures. Albeit associated with low diastereoisomeric excess, mono- and bis-alkylations of the polymer supported pyrrolidinone auxiliary (**4**) were performed with good yield and purity. By analogy with liquid phase conditions, the presence of a free hydroxy group might permit a better control of the diastereoselectivity in alkylation reactions with LDA through chelation with lithium.[4] We are therefore considering the preparation of a related (*R*)-hydroxyphenylglycinol linked auxiliary with adequate potential for structural diversity.

ACKNOWLEDGEMENTS

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10. R_f (5% MeOH in CH_2Cl_2) = 0.40 ; $[\alpha]_D^{20}$ –245 °ß(c=1 ; MeOH) ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (2H, d, J = 8 Hz), 6.75 (2H, d, J = 8 Hz), 5.00 (1H, br s), 4.15 (1H, t, J = 6 Hz), 4.05 (1H, dd, J = 2 and 7 Hz), 3.70 (2H, m), 3.60 (1H, t, J = 6 Hz), 1.40-2.10 (6H, m). ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 129.3, 128.4, 115.8, 89.7, 72.8, 63.3, 47.2, 29.9, 27.8, 19.3 ; MS calcd for $C_{14}H_{16}N_2O_2$: 244.3 ; obtained 245.
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