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Application of Radical Chemistry to Solid Support Synthesis

Sabine Berteina and Alain De Mesmaeker*

Novartis AG, CH-4002 Basel, Switzerland

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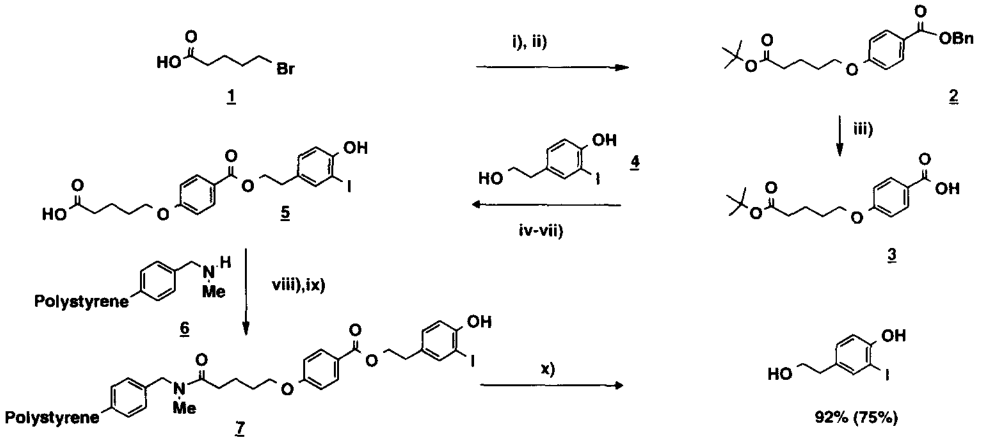
Abstract: Radical cyclization of aryl iodides bound to polystyrene is described together with the trapping of the resulting radical, prior to its reduction, by allyltributyl tin. © 1998 Elsevier Science Ltd. All rights reserved.

Combinatorial Chemistry in particularly, solid support synthesis[1] has emerged as a powerful technology to synthesize a wide variety of compounds. Although various organic reactions have been already studied on solid phase, intramolecular radical cyclization has been only mentioned twice[2a,b]. The application of radical chemistry to solid support would be very valuable for combinatorial chemistry. Under essentially neutral and mild conditions, core structures could be derivatized using intra- or intermolecular processes.

We report here some examples of the application of radical chemistry to solid support synthesis. All reactions have been performed on polystyrene[3] beads (scale 150-200mg, 0.6 mmol/g), allowing the isolation of at least 20 mg crude product. The structures were determined by ^{1}H NMR and Mass Spectroscopy and the yields refer to the weight of the crude product corrected by the purity evaluated by ^{1}H NMR (400MHz). The yields reported in parentheses are obtained after purification by flash chromatography or preparative t.l.c.

Radical cyclizations were successfully applied to the *o*-iodophenol core structure, where the aryl radical reacted on a C=C double bond to lead to the corresponding 5-exo- cyclized product. Attachment of the *o*-iodophenol moiety to polystyrene was realized through a base labile linker as outlined in **Scheme 1**.



Scheme 1. i) Isobutene, H_2SO_4 cat, CH_2Cl_2, RT, 48h (96%). ii)1.05 eq. NaH, 1 eq. *p*-HO-Ph-$COOCH_2Ph$, 1 eq. NaI, DMF, 60°C, 20h, (93%). iii) H_2 (1atm), THF, Pd-C (5%), RT, 12h, (88%). iv) 1.1 eq. $Me_2C=C(NMe_2)Cl$ (chlorenamine), CH_2Cl_2, RT, 3h. v) 0.5 eq. 4, 10 eq. pyridine, 0.2 eq. DMAP, 1.5 eq Et_3N, CH_2Cl_2, RT, 48h, (90%). vi) 10 eq. hydrazine hydrate, ethyleneglycol/dioxane (1/4) (0.1M), RT, 18h, (80%). vii) CF_3COOH/CH_2Cl_2 (1/3), RT, 22h, (90%). viii) 4 eq. 5, 4.4 eq. Et_3N, 4.4 eq. O-(1H-benzotriazole-1yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate, 2 eq. N-hydroxy-benzotriazole, dioxane, RT, 5h:

Fax : 0041 61 697 85 29
E-mail : alain.de_mesmaeker@cp.novartis.com

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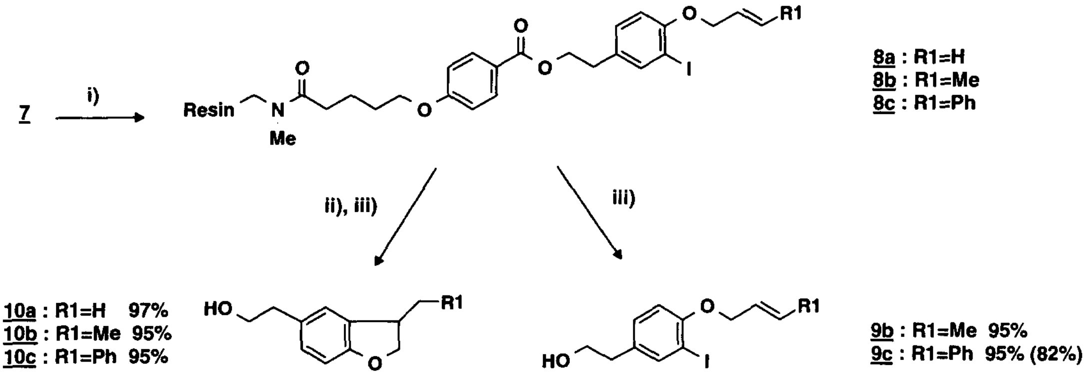
6, 10 eq. Et_3N, 1 eq DMAP, dioxane, 90h, RT. ix) 10 eq. hydrazine hydrate, ethyleneglycol/dioxane : 1/4 (0.05M), RT, 84h. x) 6 eq. MeONa, MeOH/dioxane (1/4), RT, 24h.

The selective monobenzoylation of 4[4] was not feasible. However, the benzoate group on the phenol was selectively cleaved with hydrazine to lead, after removal of the t-butylester group, to 5. The carboxylic acid 5 was connected to the solid phase 6 using the corresponding N-hydroxybenzotriazole activated ester. These conditions were superior to methods using DCC, DMAP or the corresponding acid chloride. The solid phase bound phenol 7 reacted partially with the excess of N-hydroxybenzotriazole active ester. The corresponding phenolic ester was selectively cleaved by treatment with hydrazine in the presence of ethyleneglycol without transamination of the para-alkoxy benzoate ester of the linker.

The cleavage of 7 was achieved by basic transesterification using excess sodium methoxide in a mixture of MeOH : dioxane. The overall yield of these two steps is 92%.

The cyclization substrates were prepared from 7 by treatment with the corresponding allylbromide derivatives in presence of Schwesinger base[5]. In order to assess the efficiency of the allylation, cleavage from the solid phase was systematically performed. The expected cleaved products are obtained in good yields (**Scheme 2**).



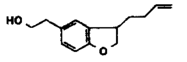
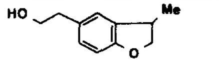
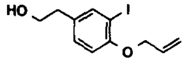
Scheme 2. i) 10 eq. R1-CH=CH-CH_2-Br, 3 eq. Schwesinger base, dioxane, RT, 24h. ii) 3 eq. nBu_3SnH, 0.6 eq. AIBN, benzene (0.05M), reflux, 46h. iii) 6 eq. MeONa, MeOH/dioxane (1/4), RT, 24h.

Cyclization of compounds 8a-c was realized using 3 eq nBu_3SnH and 0.6 eq AIBN in benzene at reflux temperature[6] to lead, after cleavage, to the expected 5-exo-cyclized products **10a-c** in very high yields. All additions of nBu_3SnH and AIBN were performed at once. Slow addition techniques were not applied here, due to potential impractibility for automation. It is noteworthy that no reduction of the radical before cyclization occurred, although numerous benzylic hydrogen atoms of polystyrene could have participated in an atom transfer reaction.

To increase molecular diversity in a single step, a radical cyclization/addition sequence could be used. Cyclization is followed by an intermolecular reaction where the cyclized radical is trapped by an allyltributyl tin derivative. The rate of allyl chain transfer being slower than the rate of hydrogen transfer from nBu_3SnH to the radical, an excess of allyltributyltin must be used. The optimization of the reaction conditions was realized on compound 8a **Table 1**.

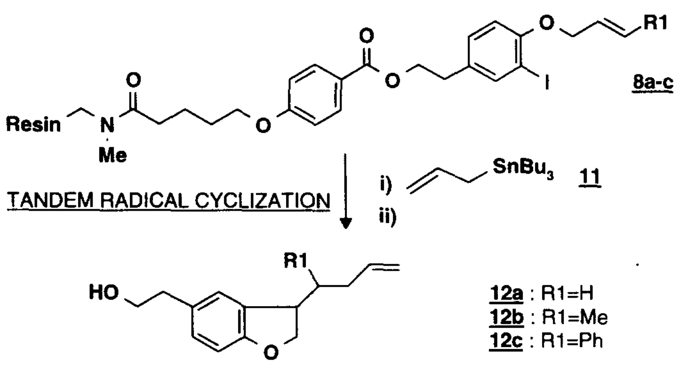
The best conditions were obtained with 15 eq. of allyltributyltin (entry 2), no further improvement was obtained with 25 eq. (entries 3-4) probably due to a lower swelling of the resin.

Tablel.

Entries	Allyl-tributyltin	Conditions[a)]			
1	10 eq.	AIBN 1.5 eq. Benzene (0.05M)	70%	24%	6%
2	15 eq.	AIBN 1.5 eq. Benzene (0.05M)	78%	22%	-
3	25 eq.	AIBN 1.5 eq. Benzene (0.05M)	37%	10%	53%
4	25 eq.	AIBN 1.5 eq. Benzene (0.025M)	49%	10%	41%

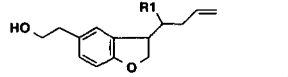
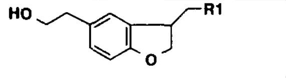
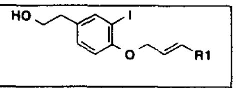
a) All reactions were performed under reflux temperature for 46h. The ratios were determined by ^{1}H NMR of the crude reaction mixture.

These experimental conditions[7] were applied to compounds 8b-c (**Scheme 3**). The results are summarized in **Table 2**. The tandem cyclization-addition procedure could be applied to solid support bound iodide even in case where the cyclized radical was further substituted by a methyl or a phenyl, although in less satisfactory yield.



Scheme 3. i) 15 eq. allyltributyltin, 1.5 eq. AIBN, benzene (0.05M), reflux, 46h. ii) 6 eq. MeONa, MeOH/dioxane (1/4), RT, 24h.

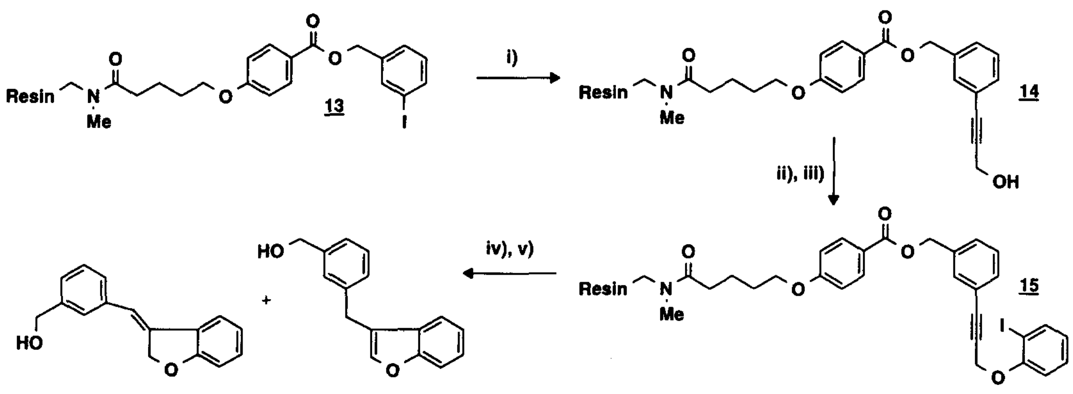
Table 2.

Entries	R1			
1	CH_3	49%	22%	29%
2	Ph	10%	10%	80%

All reactions were performed under reflux temperature for 46h. The ratios were determined by ^{1}H NMR of the crude reaction mixture.

The previous examples of radical cyclizations were performed on an aryl iodide bound to the solid support. However the C=C double bond or the C≡C triple bond could also be bound to the solid support and the aryl or vinylic iodide would be added in solution.

A first illustration of this approach is depicted in **Scheme 4**. The connection of aromatic iodide to the polystyrene was realized from the previously used base labile linker to give 13. Pd(0)-mediated coupling[8] of the aryl iodide with propargyl alcohol lead to 14 which, after treatment with chlorenamine, followed by addition of ortho-iodophenol gave the substrate for cyclization 15. The radical cyclization[6] carried out on this substrate lead to a 75/25 mixture of exo and endocyclic double bonds of the expected 5-exo cyclized compound 16 in 75% overall yield (4 steps).



16 75% overall yields (4 steps) ratio: 75/25

Scheme 4. i) 5 eq. propargylalcohol, 0.4 eq. CuI, 0.2 eq. $PdCl_2(PPh_3)_2$, Et_3N/dioxane (1/2), RT, 24h. ii) 3 eq. chlorenamine, CH_2Cl_2, RT, 5h. iii) 10 eq. *o*-iodophenol, 10 eq. Schwesinger base, 2 eq. Bu_4NBr, 60°C, 24h. iv) 3 eq. nBu_3SnH, 0.6 eq. AIBN, benzene (0.05M), reflux, 46h. v) 6 eq. MeONa, MeOH/dioxane (1/4), RT, 24h.

We have shown that 5-exo radical cyclizations can be applied to aryl iodides bound to solid support. Furthermore, the trapping of the cyclized radical was achieved with allyltributyl tin prior to its reduction. Additional examples of radical cyclization processes for the modification of core structures will be reported soon.

References and Notes

1. P.H.H. Hermkens, H.C.J. Ottenheijm, D. Rees, *Tetrahedron*, **1996**, *52*, 4527-4554; P.H.H. Hermkens, H.C.J. Ottenheijm, D. Rees, *Tetrahedron*, **1997**, *53*, 5643-5678.
2. a) A. Routledge, C. Abell, S. Balasubramanian, *Synlett*, **1997**, 61-62. b) X. Du, R.W. Armstrong, *J. Org. Chem.*, **1997**, *62*, 5678-5679.
3. Polystyrene beads, cross-linked with 1% divinyl benzene were used for all experiments.
4. The compound 4 was synthesized by treatment with NaI and Chloramine T: T. Kometani, D. S. Watt, and T. Ji, *Tetrahedron Lett.*, **1985**, *26*, 2043-2046.
5. 2-tert-Butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine : commercially available by Fluka; R. Schwesinger, H. Schlemper, *Angew. Chem.*, **1987**, 99, 1212-1214.
6. Experimental procedure: 150-200 mg resin (0.1mmol of loading substrate) was suspended in degassed benzene; then 0.5 eq. Bu_3SnH and 0.1 eq. AIBN were added. The mixture was heated to reflux temperature under an argon atmosphere. After 5 additions of 0.5 eq. Bu_3SnH and 0.1 eq. AIBN, (46h), every 5-8h, the resin was washed with benzene (6x4ml), toluene (6x4ml), hexane (6x4ml), CH_2Cl_2 (6x4ml), EtOH (6x4ml), EtOH/H_2O (1/1) (6x4ml), H_2O (6x4ml), dioxane (6x4ml), CH_2Cl_2 (6x4ml), MeOH (6x4ml), CH_2Cl_2 (6x4ml), diethyl ether (3x4ml) in order to eliminate the organotin compounds, then resin was dried under vacuum.
7. Experimental procedure: 150-200 mg resin (0.1mmol of loading substrate) was suspended in degassed benzene; then 10 eq. allyltributyltin and 0.5 eq. AIBN were added. The mixture was heated to reflux temperature under an argon atmosphere. After 5 additions of 1 eq. allyltributyltin and 0.2 eq. AIBN, (46h), the resin was washed as above.
8. S. Berteina, S. Wendeborn, W. K.-D. Brill, A. De Mesmaeker, *Synlett* in Press; for a very recent example of radical allylation reaction on solid support see: M.P. Sibi, S.V. Chandramouli, *Tetrahedron Lett.*, **1997**, *38*, 8929-8932.