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Solid-phase tandem radical addition–cyclisation reaction of oxime ethers

Hideto Miyabe, Kayoko Fujii, Hirotaka Tanaka and Takeaki Naito*

Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan. E-mail: taknaito@kobepharma-u.ac.jp

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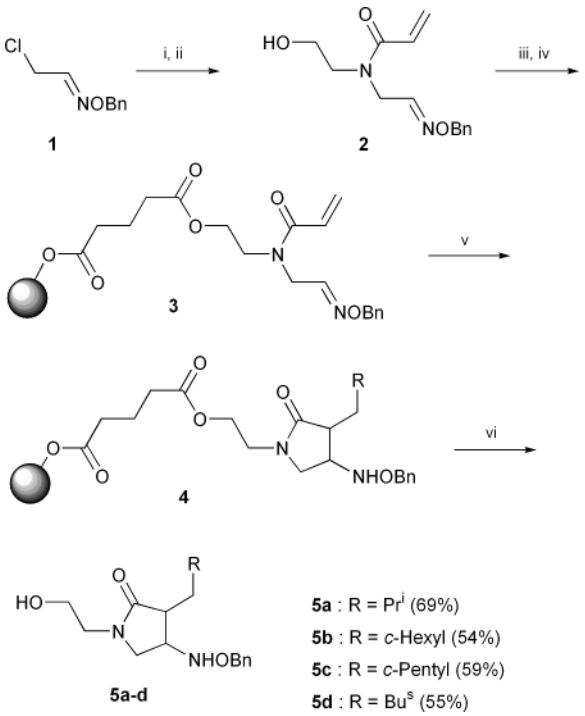
The solid-phase tandem C–C bond-forming reactions of oxime ethers connected with α,β-unsaturated carbonyl groups proceeded effectively under iodine atom-transfer reaction conditions to give the azacycles or chiral oxacycles after cleavage of the resin.

Solid-phase radical reactions have been developed for an important carbon–carbon bond-forming method on solid support under mild reaction conditions.[1] We have recently demonstrated that triethylborane as a radical initiator has the potential to induce intermolecular and intramolecular radical reactions on solid support.[2] Moreover, the employment of triethylborane and its related radical initiator such as diethylzinc at low reaction temperature would facilitate the control of stereochemistry in solid-phase reactions.[3] Within our program directed towards solid-phase radical reactions, the development of solid-phase multi carbon–carbon bond-forming reactions and their stereocontrol is the new focus of our efforts. We now report the tandem radical addition–cyclisation reaction of oxime ethers anchored to a polymer support.

In our studies on the radical reaction of various oxime ethers in solution,[4] we have recently succeeded in the solution-phase tandem radical addition–cyclisation reaction of substrates having two different radical acceptors such as acrylate and aldoxime ether moieties.[5] On the basis of the results in the solution-phase reactions, we first examined the simple solid-phase tandem radical addition–cyclisation reaction of aldoxime ether **3** connected with the α,β-unsaturated carbonyl group.

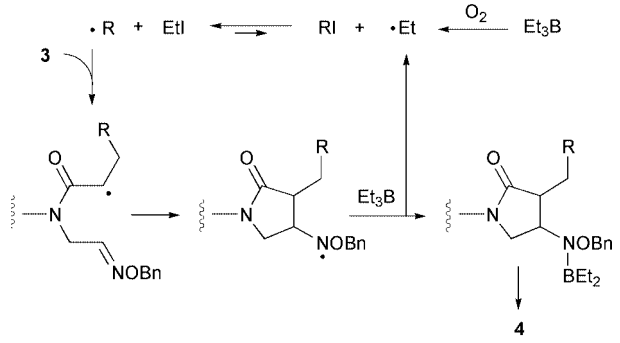
Preparation of **3** anchored to a polymer support is shown in Scheme 1. Treatment of α-chloroacetaldoxime ether **1** with 2-aminoethanol followed by acylation with acryloyl chloride gave oxime ether **2**. To enhance the reactivity of resin-bound substrate, we introduced a temporary spacer by the reaction of **2** with glutaric anhydride. The oxime ether having the spacer moiety was attached to Wang resin by treatment with DCC in the presence of DMAP to give **3**. The loading level of Wang resin-bound oxime ether **3** was determined to be 0.81 mmol g^{-1} through quantification of nitrogen by elemental analysis.

To a flask containing aldoxime ether **3** and Pr^iI (30 equiv.) in toluene a commercially available 1.0 M solution of triethylborane in hexane was added three times (3 equiv. × 3) as a radical initiator at 100 °C (Scheme 1). The reaction mixture was stirred at 100 °C for 2 h, then the resin was filtered and successively washed with CH_2Cl_2, AcOEt, and MeOH. The cleavage of the resin by treatment with NaOMe gave the desired azacyclic product **5a** in 69% isolated yield. However, the radical cyclisation of oxime ether **3** at 25 °C did not proceed.[2b] Good chemical yields were also observed in the radical reaction using different radical precursors such as cyclohexyl, cyclopentyl, and *sec*-butyl iodides under the iodine atom-transfer reaction conditions. Moreover, it is noteworthy that this iodine atom-transfer radical reaction has a practical advantage over the reaction using toxic tin reagent. A remarkable feature of these reactions is the construction of two carbon–carbon bonds on solid support under mild reaction conditions without strictly anhydrous solvents and reagents. In this reaction, triethylborane would act as a reagent for trapping the intermediate aminyl radicals to regenerate an ethyl radical; therefore, more than a stoichiometric amount of triethylborane would be required (Scheme 2).



Scheme 1 *Reagents and conditions*: i, 2-Aminoethanol, 20 °C, 88%; ii, CH_2=CHCOCl, Na_2CO_3, acetone, H_2O, 0 °C, 87%; iii, Glutaric anhydride, Py, 80 °C, 93%; iv, Wang resin, DCC, DMAP, CH_2Cl_2, 20 °C; v, RI, Et_3B in hexane, toluene, 100 °C; vi, NaOMe, MeOH, THF, H_2O, 20 °C.

Stereocontrol in solid-phase radical reactions has been of great importance in SPOS (solid-phase organic synthesis). Based on the above results, we next examined the control of stereochemistry in the solid-phase tandem radical addition–cyclisation reaction. Preparation of **10** anchored to a polymer support is shown in Scheme 3. Monoacetylation of *p*-xylene glycol, mesylation of monool with mesyl chloride in the



Scheme 2

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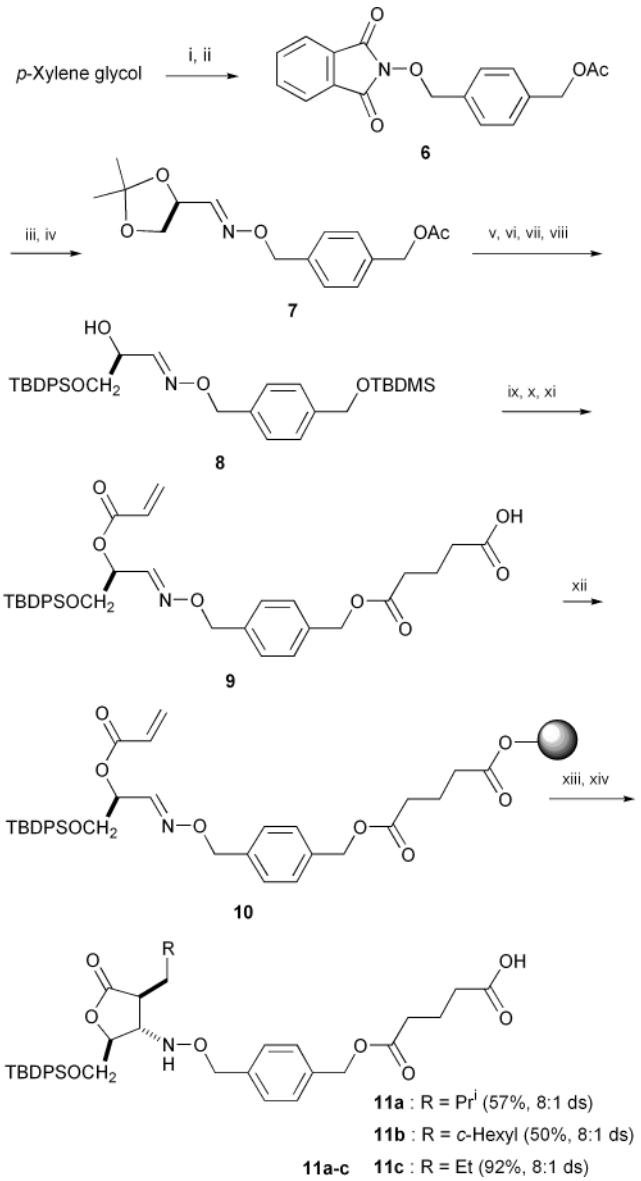

Scheme 3 *Reagents and conditions*: i, Bu^{n}Li, AcCl, THF, 0 °C, 65%; ii, MsCl, Et_3N, CH_2Cl_2, 0 °C and then *N*-hydroxyphthalimide, Et_3N, CH_2Cl_2, reflux, 71%; iii, $N_2H_4{\cdot}H_2O$, MeOH, 20 °C, 99%; iv, 2,3-isopropylidene-D-glyceraldehyde, Py, 25 °C, 73%; v, PPTS, MeOH, 65 °C, 74%; vi, TBDPSCl, imidazole, DMF, 20 °C, 75%; vii, K_2CO_3, aq. MeOH, 20 °C, 99%; viii, TBDMSCl, imidazole, DMF, 20 °C, 75%; ix, CH_2=CHCOCl, Et_3N, CH_2Cl_2, 0 °C, 65%; x, PPTS, MeOH, 65 °C, 80%; xi, glutaric anhydride, Py, 80 °C, 99%; xii, Wang resin, DCC, DMAP, CH_2Cl_2, 20 °C; xiii, Et_3B in hexane, RI:toluene = 4:1, 100 °C; xiv, TFA, CH_2Cl_2, 20 °C.

presence of triethylamine, and then treatment of the resulting mesylate with *N*-hydroxyphthalimide in one-pot afforded the imide **6** in 71% yield (Scheme 3). Treatment of **6** with hydrazine monohydrate and subsequent condensation of the resulting alkoxyamine with 2,3-isopropylidene-D-glyceraldehyde gave the chiral oxime ether **7**, which was easily converted to the secondary alcohol **8**. The reaction of **8** with acryloyl chloride followed by treatment with pyridinium toluene-*p*-sulfonate in MeOH gave deprotected benzyl alcohol, which was then treated with glutaric anhydride to give carboxylic acid **9** (Scheme 3). The carboxylic acid **9** was attached to Wang resin by treatment with DCC in the presence of DMAP in CH_2Cl_2 at 20 °C for 12 h to give the resin-bound oxime ether **10**.

The reaction of **10** with an ethyl radical proceeded effectively by treatment with triethylborane to give the chiral oxacycles **11c** in 92% yield after cleavage of the resin, which was carried out under acidic reaction conditions due to the base-sensitivity of **11c** (Scheme 3). However, the reactivity of chiral oxime ether **10** towards other alkyl radicals was quite different from that of oxime ether **3**. The treatment of **10** with Pr^{i}I (24 equiv. × 3) and triethylborane (6 equiv. × 3) in toluene at 100 °C gave a large amount of the ethylated product **11c** and a small amount of the isopropylated product **11a** after cleavage of the resin. This result suggests that, in this reaction, the addition of ethyl radical, generated from triethylborane, competes with the iodine atom-transfer process because triethylborane, having Lewis acidic character, probably coordinates the substrate on the polymer-support and is concentrated on the surface of the resin. A similar trend has been observed in our previous studies.[3] Selective formation of the desired isopropylated product **11a** was observed in the reaction of **10** (50 mg) using triethylborane (5.9 equiv. × 3) in Pr^{i}I–toluene (4:1, v/v, 5 mL) at 100 °C. Based on ^{1}H-NMR analysis, a 8:1 diastereomeric mixture of the isopropylated oxacyclic product **11a** was obtained in 54% isolated yield. Additionally, in the solid-phase reactions, the often tedious workup to remove excess reagents from the reaction mixture was eliminated simply by washing the resin with solvents. The addition of a bulky cyclohexyl radical proceeded in slightly low chemical efficiency under the same reaction conditions to give the alkylated product **11b** but with a similar diastereoselectivity.

In conclusion, we have demonstrated that tandem radical reactions are an excellent method for the stereoselective construction of multi carbon–carbon bonds on solid support.

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