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First organophosphorus radical-mediated cyclisations to afford medium-sized rings: eight-membered lactones and seven- and eight-membered lactams

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Abstract—The phosphorus based radical precursors *N*-ethylpiperidine hypophosphite (EPHP) and diethylphosphine oxide (DEPO) are efficient reagents for carrying out the formation of seven- and eight-membered rings. Esters and amides were successfully converted into the corresponding eight-membered lactones and seven- and eight-membered lactams in good to excellent yields.

There is a strong impetus within the radical community to develop new and efficient alternatives to the commonly used neurotoxic radical chain carrier tributyltin hydride (TBTH). The toxicity associated with the organotin residues together with the difficulties that are encountered when removing these by-products[1] from the desired compound means that organotin reagents cannot be used for the manufacture of pharmaceuticals. Tristrimethylsilylsilane[2] (TTMSS) is a popular alternative to TBTH displaying similar, although not identical, reactivity. The main drawback of TTMSS is the high cost, making large-scale use impractical. Alternative radical sources however have shown considerable promise.[3,4]

Among the more recent developments, phosphorus based chain carriers have been proposed as a less costly class of reagent for the radical mediated formation of C–C bonds. Some of the phosphorus reagents to obtain notable success are hypophosphorous acid[5] and its sodium salt,[6] *N*-ethylpiperidine hypophosphite (EPHP),[7] diethyl phosphite[8] and more recently, diethylphosphine oxide (DEPO),[9] recently cited as a useful reagent for process R&D chemistry.[10] A key point with the phosphorus reagents is the strength of the P–H bond; a strong bond potentially allows observation of slower radical processes (cyclisations, fragmentations, intermolecular additions, etc.) that depend on intermediate radicals not being prematurely quenched.

An untested area for these reagents is the formation of medium-sized rings. We now report the first cyclisations to form seven- and eight-membered rings using phosphorus based radical reagents.

Our substrates were bromoesters and bromoamides. Bromoesters **1** abound with opportunities for alternative reactions to compete with the desired ring formation. Phosphorus-centred radicals add easily to alkenes, particularly to terminal alkenes;[8] indeed, this type of reaction has been widely used in synthesis. In this case radical **5** would result. This process could interfere with the abstraction of Br by the phosphorus radical en route to radical **2**. If formation of **2** is successful, reduction of the α-acyl radical **2** could occur by hydrogen abstraction from the phosphorus reagent to afford ester **3** or, alternatively, 5-*exo*-trig cyclisation onto the arene could occur to give radical **4**, which in turn could lead to benzofuranone products (Scheme 1).[11]

Hence, these simple substrates should prove useful indicators of the applicability of the phosphorus reagents in a more rigorous synthetic setting [i.e., synthesis of

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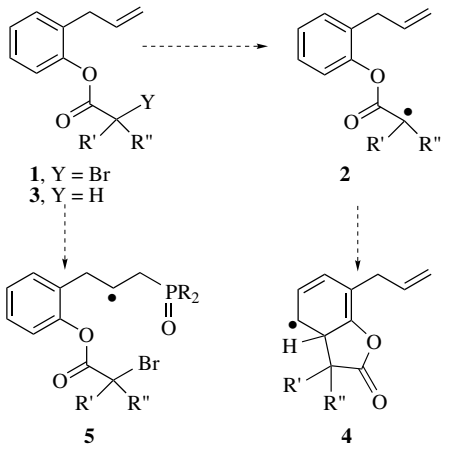
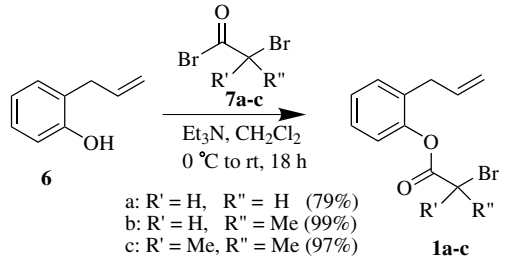


Scheme 1.

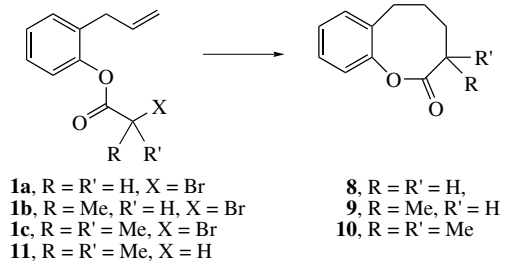


Scheme 2. Generation of bromoester substrates **1a**–**c**.

seven- and eight-membered rings] than the conventional five-membered ring formation.[9]

Treating commercially available phenol **6** with the appropriate α-bromoacyl bromides **7a**–**c**, allowed easy access to the desired esters **1a**–**c** in excellent yields (Scheme 2).

When **1a** was subjected to phosphorus radicals, generated either by exposure of EPHP (*N*-ethylpiperidinium hypophosphite) (10 equiv)[12] or DEPO [diethylphosphine oxide, $Et_2P(O)H$] (10 equiv)[13] to VAZO® initiator 88[14a] [1,1′-azobiscyclohexanecarbonitrile] in refluxing toluene (Scheme 3 and Table 1), encouragingly eight-membered lactone **8** was formed[15] in excellent yields [65% and 80%, respectively], with no seven-membered ring products and no products of undesired side-reactions being observed.



Scheme 3. Cyclisation of bromoester substrates **1a**.

Table 1. Phosphorus radical cyclisations of esters **1a**–**c**

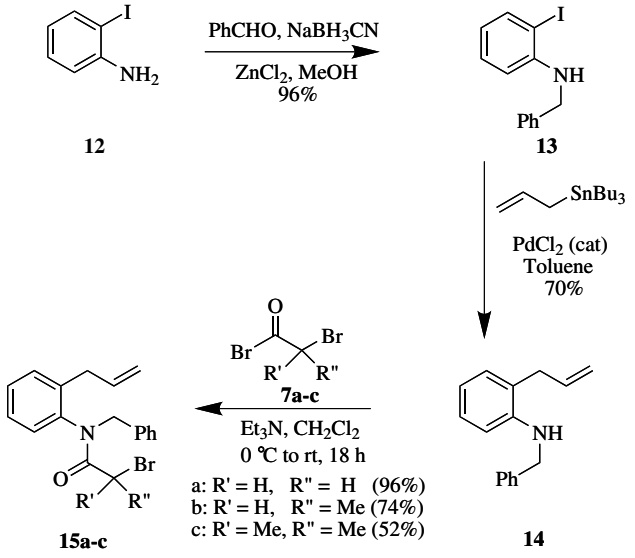
Substrate	Cyclised product (%)	Reduced product
1a[a]	**8** (65)	—
1a[b]	**8** (80)	—
1b[a]	**9** (75)	—
1b[b]	**9** (91)	—
1c[a]	**10** (89)	—
1c[b]	**10** (64)	—

[a] EPHP, VAZO 88, PhMe, Δ.[12]
[b] DEPO, VAZO 88, PhMe, Δ.[13]

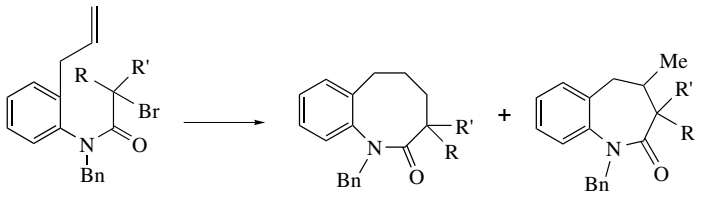
Similarly, bromoester **1b** gave lactone **9** as the only product formed in the reaction (Table 1). The final ester substrate, **1c**, also cleanly cyclised, forming lactone **10** under both sets of conditions, with no other products being observed in the reaction mixture. For comparison, bromoester **1c** was also reacted under the standard tin-based radical conditions of TBTH and VAZO® initiator 88 in refluxing toluene. Surprisingly, this gave a complex mixture that could not be purified.

Having explored the reactions of these esters in organic solvents, reactivity in water was next explored. Oshima and co-workers had shown[5d] dramatic changes in regioselectivity in hypophosphite-mediated cyclisations of ester-derived radicals when conducted in water. Hence the cyclisation reaction was now tried—on substrate **1b** only—under aqueous conditions.[16] This reaction was not successful, with phenol **6** being the only identifiable compound formed due to hydrolysis of the ester starting material.

Although the EPHP and DEPO reagents are both phosphorus based, they have very different reactivities. For example, the DEPO reactions are carried out without the need for a syringe pump, but a syringe pump is routinely required for the EPHP reactions; this is in line with previous evidence[9] that DEPO features a stronger P–H bond. When **1c** was treated under the EPHP



Scheme 4. Route to form bromoamide **15a**–**c**.



15a, R = R' = H, X = Br
15b, R = Me, R' = H, X = Br
15c, R = R' = Me, X = Br

16, R = R' = H,
17, R = Me, R' = H
19, R = R' = Me

18, R = Me, R' = H
20, R = R' = Me

Scheme 5. Radical cyclisations of bromoamides **15a–c**.

conditions without a syringe pump, a 2:1 mixture of cyclised product **10** and reduced product **11** was formed.

With these initial excellent results, our attention turned to the formation of lactams. Benzylation of 2-iodoaniline **12** gave benzylaniline **13**. Stille-based allylation[17] afforded allyl derivative **14**, which was then exposed to acid bromides **7a–c**. This furnished amides **15a–c** in a simple three-pot procedure (Scheme 4).

The behaviour of amide **15b** was first examined. Reaction with DEPO in toluene[13] led to the 8-*endo* product **17** but only in 32% yield; the major product was the 7-*exo* product **18**, which was formed in 65% yield (Scheme 5). The efficiency of the cyclisation process was again gratifying, but the observation of 7-*exo* product **18** was reminiscent of results obtained[15b] by Ikeda and co-workers, using tributyltin hydride in organic solvents on different but related substrates.

This reaction was also carried out using the EPHP conditions[12] and gave rise to identical yields of amides **17** and **18**. Carrying out the reaction in water[16] using DEPO as the radical reagent precursor along with the water-soluble initiator VA-501[14a] [4,4′-azobis-4-(cyanovaleric acid)] gave a slightly higher yield of 8-*endo* product **17** (43%).

These aqueous DEPO radical reactions were then used for the cyclisations of amide **15a**, which afforded 8-*endo* product **16** in 46% yield as the only isolated compound. Amide **15c** was then subsequently exposed to these conditions, giving rise to 8-*endo* product **19** (31%) and 7-*exo* product **20** (39%). Hence, even conducting these reactions in water[5d] did not lead to any notable regiochemical differences compared to using toluene as solvent (Table 2).

The results above show that formation of α-acyl radicals occurs more rapidly than addition of the phosphorus radicals to the terminal alkene of the allyl group. In turn the α-acyl radical shows preferential cyclisation onto the alkene (7-*exo* and 8-*endo*) rather than onto the disubstituted aryl ring. This is not too surprising for the ester-derived radicals[15c] in organic solvents. However, for the amide-derived radicals, we have recently shown[9] how favourable this cyclisation can be under our DEPO conditions (although Beckwith et al. have shown[18] that this cyclisation can be difficult with trialkyltin chain carriers). Cyclisation onto the phenyl group of the benzyl ring was not observed; such a cyclisation was unlikely, due to the preferred conformations[19] of the amide.

Table 2.

Substrate	8-*endo*-Trig product (%)	7-*exo*-Trig product (%)
15a[a]	**16** (46)	—
15b[b]	**17** (32)	**18** (65)
15b[c]	**17** (32)	**18** (65)
15b[a]	**17** (43)	**18** (50)
15c[a]	**19** (31)	**20** (39)

[a] DEPO, VA-501, H_2O.[16]
[b] EPHP, VAZO 88, PhMe, Δ.[12]
[c] DEPO, VAZO 88, PhMe, Δ.[13]

Comment must be made on the different levels of selectivity seen for the formation of lactones versus lactams. Computational studies[20] on the α-acyl radical derived from **1c** suggest that the transition state for cyclisation to form the eight-membered ring is about 29 kJ/mol lower in energy than that leading to seven-membered ring, supporting the total selectivity observed experimentally. However, the more complex computation on the radical derived from amide **15c** shows more than one low-energy conformation, some of which favour 7-*exo*-trig cyclisation while some favour eight-*endo*-trig cyclisation, again supporting experimental observations.

In summary, it has been shown that both EPHP and DEPO can be employed for radical based direct formation of seven- and eight-membered rings. There is no premature reduction of the intermediate radicals by the phosphorus reagents, and addition of phosphorus radicals to terminal alkenes does not cause any problems. In the case of DEPO, the reactions are performed without the need for a syringe pump, again attesting to the intriguing properties of this reagent. Work is currently continuing in our laboratories to study the basis of selectivity in these reactions.

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11. See however Ref. 15c, which suggests that this is unlikely for the ester substrates.
12. Typical EPHP experimental procedure: 1-EPHP (3.59 g, 20.0 mmol, 10.0 equiv) and VAZO 88 (196 mg, 0.8 mmol, 0.4 equiv) in dry toluene (10 mL) were added, via a syringe pump over 10 h, to a stirred solution of substrate (2.0 mmol, 1 equiv) in dry toluene (200 mL). After addition was complete, the reaction was left to stir for 1 h. The reaction was cooled and the solvent was removed under reduced pressure. The residue was dissolved with EtOAc (50 mL) and washed with water (100 mL), $NaHCO_3$ solution (100 mL), 1 M HCl (100 mL) and washed with brine (100 mL). The organic layer was dried, filtered and the solvent removed and purified by column chromatography (silica: 5–10% EtOAc in heptane) to afford the desired lactone/lactam.
13. Typical DEPO in organic solvent experimental procedure: Toluene (10 mL) was boiled for 10 min under nitrogen, then the substrate [1 equiv (0.04–0.86 mmol)] and DEPO (10 equiv) were added. VA-501 (0.5 equiv) was added after 5 min and the mixture was heated for 6 h at 80 °C. VA-501 (0.5 equiv) was added again and mixture was further heated for 6 h. The mixture was cooled and NaOH soln (2 N, 15 mL) added and then finally the mixture was extracted with Et_2O (30 mL). The organic layer was dried, filtered and concentrated in vacuo. The mixture was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (90/10–85/15) to afford the desired lactone/lactam.
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16. Typical DEPO in water experimental procedure: Water (3–4 mL) was boiled for 10 min under nitrogen and then the substrate [1 equiv (0.04–0.86 mmol)] and DEPO (10 equiv) were added. VA-501 (0.5 equiv) was added after 5 min and mixture was heated for 6 h at 80 °C. VA-501 (0.5 equiv) was added again and mixture was further heated for 6 h. The mixture was cooled and sodium hydroxide (2 N, 15 mL) was added and then finally the mixture was extracted with diethyl ether (20 mL × 3). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The mixture was purified by column chromatography on silica gel using petroleum ether/EtOAc (90/10–85/15) to afford the desired lactam.
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