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Synthesis of phosphine oxide based amphiphilic molecules *via* ring-opening Wittig olefination of a macrocyclic phosphoranylidene and their property study as non-ionic surfactants†

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A novel ring-opening Wittig olefination approach was developed for the synthesis of amphiphilic phosphine oxides (PO) as non-ionic surfactants. The approach concurrently introduces the crucial functional groups (lipophilic chain and phosphine oxide moiety) present in the known PO surfactants and additional hydrophilic group (*i.e.*, ethylene glycol units) in one step *via* Wittig olefination of a macrocyclic phosphoranylidene. A series of novel PO compounds were obtained from a variety of aldehydes and selected compounds were examined for their physicochemical properties (surface tension, critical micelle concentration and interfacial tension) and also for their abilities to form emulsions as non-ionic surfactants.

Introduction

Wittig olefination involving stabilized phosphorus ylides is a well-known chemical reaction as an efficient and robust C–C coupling strategy for organic synthesis^{1–3} as well as for protein bio-conjugation and labelling.^{4,5} However, the traditional scope of this reaction predominantly targets the synthesis of olefinic products wherein the phosphorus ylide works as an activation group only and phosphine oxide is generated as a by-product (Fig. 1, I), resulting in poor atom efficiency. A few exceptions were reported by Zhou's group who made use of the waste phosphine oxide in tandem reactions wherein it was generated from the first step Wittig reaction and sequentially worked as catalyst/co-catalyst in the next stereo-selective reaction step.⁶ In our efforts in developing green and efficient synthesis of specialty chemicals, we were inspired by a class of phosphine oxide (PO) based non-ionic surfactants.⁷ These PO surfactants, exemplified by alkyl dimethyl (CnDMPO) and alkyl diethyl (CnDEPO) phosphine oxides with typically C8–C14 alkyl chain (Fig. 2), have recently attracted renewed interests owing to their excellent detergency properties and potential industrial applications as surfactants/emulsifiers.^{7–9} Conventional PO based amphiphilic molecules contain only phosphine oxide as their hydrophilic heads, and their synthesis involve the preparation of a Grignard reagent

dialkylphosphinylmagnesium bromide from diethyl phosphonate followed by further alkylation using alkyl bromide (Fig. 2).¹⁰ This method uses flammable Grignard reagent, and the target molecules have limited structural diversity. We envisioned that diversification for this family of surfactants can be conveniently achieved by utilizing a Wittig olefination strategy, which involves a macrocyclic phosphoranylidene intermediate (Fig. 1, II). This ring-opening Wittig olefination approach not only enables the convergence of two different molecular architectures, but also concurrently introduces a required phosphine oxide functionality and imparts additional hydrophilic group, *i.e.*, oligomeric ethylene glycol, into the structure of the surfactant which further increases its hydrophilicity, and hence could potentially promote its surfactant properties. In this work, we examined the route for the synthesis of macrocyclic phosphoranylidenes and the following ring-opening Wittig reactions with a variety of aldehydes.

Results and discussion

As a proof of concept for the synthesis of a macrocyclic triphenyl phosphoranylidene, we began with the synthesis of cyclic

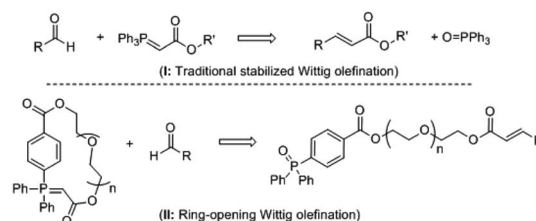


Fig. 1 Traditional Wittig olefination (I) and modified ring-opening Wittig olefination from a macrocyclic triphenyl phosphoranylidene (II).

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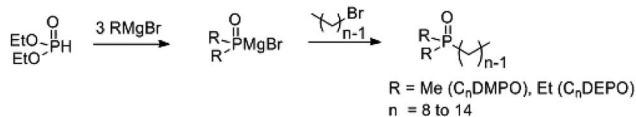
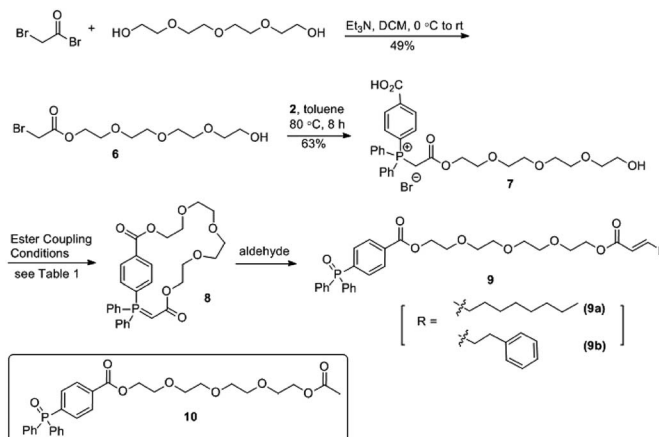


Fig. 2 Synthesis of alkyl dimethyl (CnDMPO) and alkyl diethyl (CnDEPO) phosphine oxides.¹⁰

phosphoranylidene **4a** which bears a hexyl chain as linker. 6-Bromohexyl 2-bromoacetate (**1a**) and 1,4-diphenylphosphinobenzoic acid (**2**) were initially employed for this purpose. While the insertion of the bromoacetate **1a** to **2** by heating (80 °C) in toluene provided the phosphonium salt **3a** successfully (Scheme 1), the cyclization reaction of **3a** to form cyclic phosphoranylidene **4a** failed to proceed under various basic conditions (*i.e.*, Et₃N, *i*Pr₂NEt, K₂CO₃ and *t*BuOK). Considering the hexyl chain might not be sufficiently long for the cyclization to take place, nonyl bromoacetate (**1b**) was studied next.¹¹ Indeed, cyclic triphenyl phosphoranylidene **4b** was successfully obtained from triphenylphosphonium salt **3b** upon base-mediated macrolactonization. The formation of **4b** was confirmed by mass spectroscopy and subsequent formation of the Wittig olefination product **5** from 3-chlorobenzaldehyde in one pot, albeit in low yield (13%). By-product **5a** (17%) was also isolated together, indicating the cyclization reaction was incomplete. Nevertheless, this demonstrated for the first time the reaction of ring-opening Wittig olefination of a cyclic phosphoranylidene.

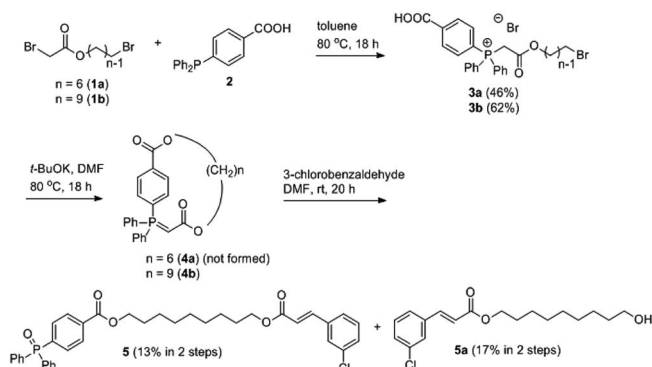
Taking into account that the presence of a hydrophilic moiety is required for the amphiphilicity of a non-ionic surfactant, tetraethylene glycol was introduced into the next synthesis as the spacer replacing the nonyl group (Scheme 2), wherein the cyclization method was also improved. The synthesis of the target molecule **9** commenced with the acylation of tetraethylene glycol with bromoacetyl bromide, which provided compound **6** in 49% yield. Heating bromide **6** with 4-(diphenylphosphanyl)benzoic acid **2** provided the triphenylphosphonium salt **7** in a similar fashion. The initial attempt of macrocyclization *via* esterification was carried out using EDC/HOBt as coupling reagent. Similar to the result for the synthesis of **4b** (Scheme 1), the formation of the desired cyclic phosphorus ylide **8** was confirmed by both MS and NMR analyses of the crude product. However purification of **8** by column



Scheme 2 Synthesis of **9a** and **9b** *via* ring-opening Wittig olefination.

chromatography became a challenge. Further examination of the crude product revealed that the cyclic ylide **8** was unstable and readily hydrolysed by the ambient water to produce the undesired ring-opening phosphine oxide **10** (Scheme 2). Non-stabilized phosphorus ylide is known to undergo alkaline hydrolysis or alcoholysis to form alkane/arene and phosphine oxide.^{12–14} However such hydrolysis/alcoholysis rarely happens for stabilized ylides due to its lower pK_a as compared to water and alcohol, and indeed, Wittig olefinations carried out in aqueous media were commonly reported for linear stabilized phosphoranylidenes.^{3–5} The instability of ylide **8** towards hydrolysis is likely due to the conformational strain imposed on its P=C bond within the cyclic system. It is interesting that recently Byrne's group reported a new mechanism for the phosphorus ylide hydrolysis *via* concerted addition of O–H bond to P=C bond, which is particularly applicable to more acidic (or more stabilized) phosphorus ylide.^{15,16} Such degradation mechanism could explain the hydrolysis of **8** under ambient condition.

With this understanding, we next carried out the cyclisation and Wittig olefination reactions in one-pot without isolating the phosphoranylidene **8**. However, the intramolecular coupling of **7** using EDC/HOBt/K₂CO₃ was inefficient and gave the Wittig products **9a** and **9b** in only 17% and 14% yields from nonanal and 3-phenylpropionaldehyde respectively in two steps (Entry 1 of Table 1). The use of organic base *i*Pr₂NEt instead of K₂CO₃



Scheme 1 Synthesis towards a cyclic triphenylphosphoranylidene **4** and its olefination.

Table 1 Optimization of intramolecular cyclization of **7** and the yields of Wittig olefination with nonanal and 3-phenylpropionaldehyde in two-step one-pot reactions

Entry	Coupling condition	Yield of 9a (%)	Yield of 9b (%)
1	EDC, HOBt, K ₂ CO ₃ , DCM, rt, 16 h	17	14
2	PyBOP, Cs ₂ CO ₃ , DCM, rt, 16 h	36	29
3	PyBOP, Cs ₂ CO ₃ , DMF, rt, 4 h, then 40 °C upon addition of aldehyde	63	74



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Table 4 Interfacial tension of water/*n*-decane phase in the presence of surfactants (conc at 0.04 wt%) at 25 °C^a

Entry no	Sample	IFT (mN m ⁻¹)
1	9a	12.65 ± 0.50
2	9e	15.08 ± 0.47
3	9f	11.73 ± 0.33
4	11	2.97 ± 0.04

^a IFT of water/*n*-decane (at 25 °C) is 52 mN m⁻¹.¹⁹

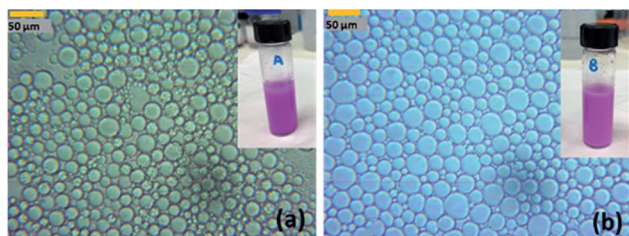


Fig. 3 Optical microscopic (40×) and camera images taken after fresh preparation of emulsions *via* ultrasonic homogenization. (a) **9a**/water/*n*-decane; (b) **11**/water/*n*-decane (both with rhodamine dye for better visualization).

that the three PO surfactants can reduce IFT of the system in approximately 3.5–4 fold as compared to that without surfactant (52 mN m⁻¹), although weaker than reference compound **11**.

Surfactant **9a** was further studied for its emulsification ability and compared with that of ref. **11**. The biphasic mixture of water/*n*-decane (1 : 1) containing surfactant and rhodamine dye was homogenized using ultrasonic homogenizer for five minutes and the resulting emulsion was visualized by camera as well as optical microscopy. As shown in Fig. 3, both surfactants gave rise to emulsions with droplet size at micrometer range, albeit the emulsification by **9a** is less efficient than that by **11**, with a layer of *n*-decane still present at the top (Fig. 3a).

Conclusions

In summary, we have here demonstrated for the first time the reaction of ring-opening Wittig olefination of a cyclic phosphoranylidenes, from which a convenient and efficient approach for the synthesis of novel functional phosphine oxides based amphiphilic molecules was developed. Preliminary physicochemical studies of selected compounds (**9a**, **9e**, **9f**) showed that they possess good surfactant properties and were capable of forming emulsion in a biphasic water/*n*-decane system, although further work remains to be done in terms of in depth property evaluation and structure-activity relationship studies. In the context of recently rekindled interest in the development of more advanced PO surfactants, the strategy we have developed here opens a new avenue for constructing novel scaffold of PO based surfactants.⁷

Conflicts of interest

There are no conflicts to declare.

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