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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 physiochemical 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 bioconjugation 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

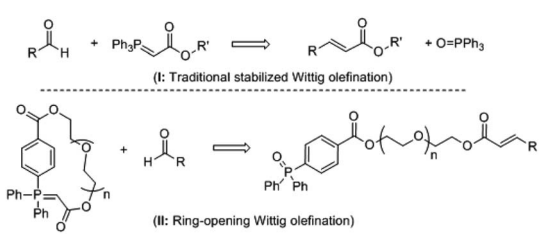

Fig. 1 Traditional Wittig olefination (I) and modified ring-opening Wittig olefination from a macrocyclic triphenyl phosphoranylidene (II).

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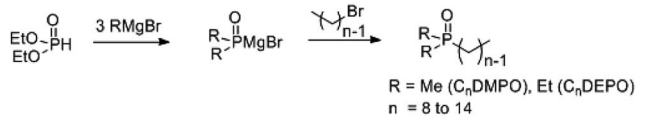
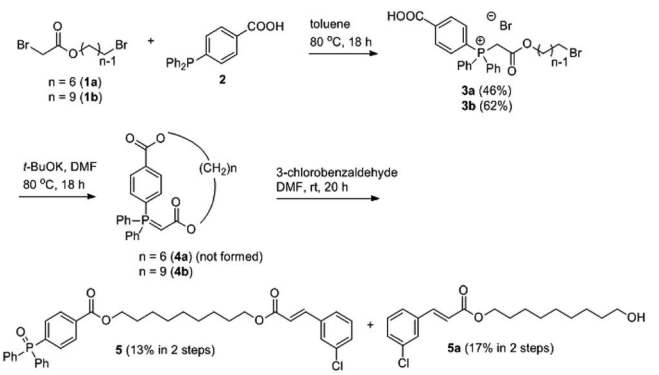


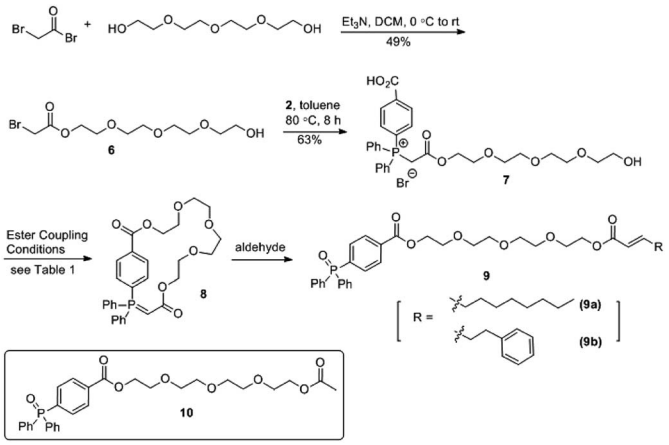
Fig. 2 Synthesis of alkyl dimethyl (CnDMPO) and alkyl diethyl (CnDEPO) phosphine oxides.[10]

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.*, Et_3N, *i*Pr_2NEt, K_2CO_3 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-(diphenylphosphaneyl)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 1 Synthesis towards a cyclic triphenylphosphoranylidene **4** and its olefination.



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

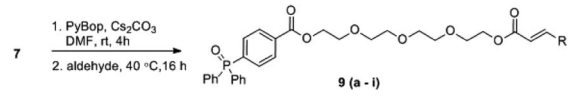
chromatography became a challenge. Further examination of the crude product revealed that the cyclic ylide **8** was unstable and readily hydrolysed by the ambient water to produce the undesired ring-opening phosphine oxide **10** (Scheme 2). Non-stabilized phosphorus ylide is known to undergo alkaline 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.

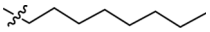
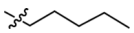
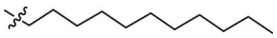
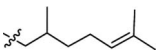
With this understanding, we next carried out the cyclisation and Wittig olefination reactions in one-pot without isolating the phosphoranylidene **8**. However, the intramolecular coupling of **7** using EDC/HOBt/K_2CO_3 was inefficient and gave the Wittig products **9a** and **9b** in only 17% and 14% yields from nonanal and 3-phenylpropioaldehyde respectively in two steps (Entry 1 of Table 1). The use of organic base *i*Pr_2NEt instead of K_2CO_3

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

Entry	Coupling condition	Yield of **9a** (%)	Yield of **9b** (%)
1	EDC, HOBt, K_2CO_3, DCM, rt, 16 h	17	14
2	PyBOP, Cs_2CO_3, DCM, rt, 16 h	36	29
3	PyBOP, Cs_2CO_3, DMF, rt, 4 h, then 40 °C upon addition of aldehyde	63	74

Table 2 One-pot ring-opening Wittig olefination of various aldehydes



Product	Aldehyde substrate	R	Isolated yield (%)
9a	Nonanal		63
9b	3-Phenylpropioaldehyde		74
9c	Hexanal		71
9d	2-Methyl valeraldehyde		48
9e	Dodecanal		63
9f	(±)-Citronellal		61
9g	4-Cyanobenzaldehyde		64
9h	4-Anisaldehyde		72
9i	Pivalaldehyde		Not isolated

did not increase the yield. Upon switching coupling reagents to PyBOP/Cs_2CO_3, the yields of the same products **9a** and **9b** increased to 36% and 29% respectively (Entry 2). Further optimization of the reaction under slightly elevated temperature (40 °C) for Wittig olefination using DMF as the solvent improved the yields to 63% and 74% respectively (Entry 3).

We next extended the substrate scope by subjecting a variety of aliphatic and aromatic aldehydes bearing different chain lengths, branches as well as electronic property to the ring-opening Wittig olefination. As shown in Table 2, linear aldehydes without substitution at 2-position gave higher yields than those with methyl substitution (71% of **9c** *vs.* 48% of **9d**), and no product of **9i** was isolated from reaction with pivalaldehyde. This result is in consistent to the report that carbonyls with more steric hindrance work less efficiently in Wittig olefination.[1] For comparison, substitution at 3-position (**9f**, 61% yield) rendered less influence on the reaction. Aldehydes with a longer aliphatic chain appeared less efficient than that with shorter chain (63% of **9a** *vs.* 71% **9c**) but this effect became marginal when the chain was further elongated (**9a** *vs.* **9e**). The electronic property on the aromatic aldehydes seems to have no significant influence on their reactivity (**9g** *vs.* **9h**), which is out of our expectation that aromatic aldehyde with electron-withdrawing group (**9g**) should be more reactive toward attacking the carbon anion of ylide **7** than that with electron-donating substitution (**9h**). This could indicate that the role of steric effect of the aldehyde overcomes its electrophilicity in the efficacy of Wittig olefination here.

Having demonstrated a convenient route to novel phosphine oxides, compounds **9(a,e,f)** (with longer lipophilic chain) were selected based on the estimated hydrophile–lipophile balance (HLB) values[17] as potential non-ionic surfactants for physiochemical properties studies, *i.e.*, surface tension, critical micelle concentration (CMC), interfacial tension (IFT), as well as the emulsification ability.

The surface tensions of the three compounds in aqueous phase were measured by tensiometry, and their critical micelle concentration (CMC) values were determined by plotting the curve of surface tension *versus* the logarithm of the concentration of the aqueous surfactant solution and the results are summarized in Table 3. The commercial non-ionic surfactant, polyoxyethylene monostearate (**11**) which contains ethylene glycol and alkyl units was used as reference for comparison of physiochemical properties. The measured CMC values of these synthetic surfactants fall within the reasonable range of a typical non-ionic surfactant CMC at about $\times 10^{-4}$ M and close to that of **11**.[18] Their surface tensions at CMC (γ_{CMC}) follow the similar trends of those known PO surfactants (CnDMPO) in that the surfactant having the lowest mass in hydrophobic chain (**9a**) gives the highest surface tension.[7] Compound **9e** shows the best surface activity with lowest surface tension (γ_{CMC}: 39.2 mN m^{-1}) at CMC among the three, and is closer to that of the reference sample (**11**, γ_{CMC}: 36.4 mN m^{-1}).

The effect of surfactants to the interfacial tension (IFT) of a biphasic system was studied in water/*n*-decane interface for **9(a,e,f)** and **11**, the IFT values are listed in Table 4. It was shown

Table 3 Surface activity data for surfactants **9a**, **9e**, **9f** and reference non-ionic surfactant **11**

Compound	γ_{CMC} (mN m^{-1})	CMC (mmol L^{-1})
9a	42.9	0.291
9e	39.2	0.532
9f	40.6	0.591
11	36.4	0.184

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]

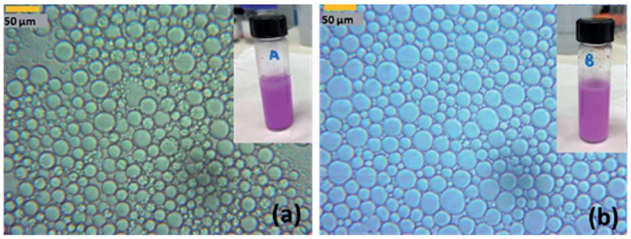


Fig. 3 Optical microscopic (40×) and camera images taken after fresh preparation of emulsions *via* ultrasonic homogenization. (a) **9a**/water/*n*-decane; (b) **11**/water/*n*-decane (both with rhodamine dye for better visualization).

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 phosphoranylidene, 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.

Acknowledgements

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