One-Pot Synthesis of New 6-(Alkylamine)Dibenzo[*c,e*][1,2]Oxaphosphinine-6-Oxides

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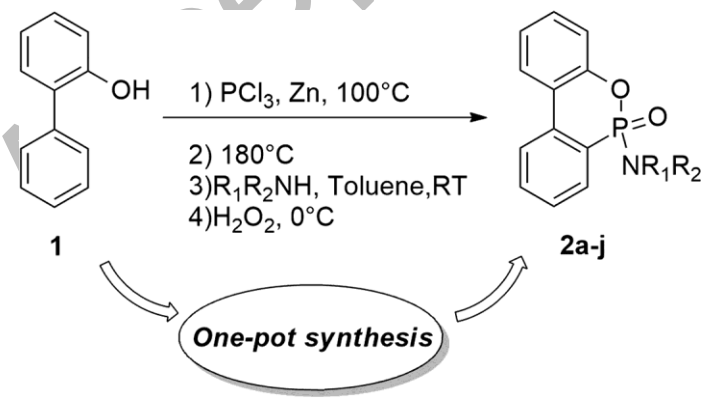
Abstract

Several new 6-(alkylamine)-6*H*-dibenz[*c,e*][1,2]oxaphosphinine-6-oxides were prepared via a *one-pot* reaction, starting with 2-phenylphenol, phosphorus trichloride, and a Zn catalyst, to form 6-chloro-6*H*-dibenz[*c,e*][1,2]oxaphosphine. The alkylamine derivatives were subsequently prepared via a Nucleophilic Substitution (SN) reaction involving aliphatic amines and H2O2 oxidation under soft conditions. This method has the advantages that it is a *one-pot* synthesis, does not require an inert atmosphere, and involves *in-situ* catalyst formation.

Graphical Abstract



KEYWORDS: oxaphosphine oxides, *one-pot* synthesis, alkylamine, *in-situ* catalyst

Introduction

Derivatives of 6H-dibenz[c,e][1,2]oxaphosphinine-6-oxides are of great interest due to their potential applications as flame retardants in polymer systems.[1–3] Among these compounds, the 6-(alkylamine)-6H-dibenz[c,e][1,2]oxaphosphinine-6-oxides are of particular interest on account of their low toxicity compared with polyhalogenated compounds used as flame retardants.[4] Despite the interesting properties of 6H-dibenz[c,e][1,2]oxaphosphinine-6-oxides, only a few methods for synthesizing these compounds have been reported in the literature.[5–7] One synthesis starts with 6-chloro-dibenzo[c.e][1,2]oxaphosphorine (CDOP)[5,6] and, after two steps, the 6-diethylamino-dibenz[c,e][1,2]oxaphosphinine-6-oxide is obtained in good yield; the disadvantage of this method is that a series of steps are required to prepare the CDOP starting materials. Another method starts from 6H-dibenz[c,e][1,2]oxaphosphinine-6-oxide (DOPO),[7] which is commercially available. This method uses the Atherton-Todd reaction[8] and offers good results; however it has not been extensively explored. Here we describe the first one-pot synthesis of 6-(alkylamine)-6H-dibenz[c,e][1,2]oxaphosphinine-6-oxides, starting from the commercially available and inexpensive compound, 2-phenylphenol.

RESULTS AND DISCUSSION

Taking into account that CDOP and DOPO (the starting materials for the previously reported syntheses of our target compounds) can be obtained from 2-phenylphenol, we considered the possibility of obtaining the 6-(alkylamine)-6H-

dibenz[c,e][1,2]oxaphosphinine-6-oxides **2** (Scheme 1) in a one-pot process from 2-phenylphenol **1**. In our first attempt at this synthesis, 2-phenylphenol was first reacted with PCl_3 at 50°C[5] without solvent. After 3 h, 40 mol % of $ZnCl_2$ was added and the temperature was increased to 150°C and the mixture was stirred for 2 h. Then, the solution was cooled to R.T. and a solution of diethylamine in toluene was added and the mixture was stirred for 3 h. The solution was then cooled to 0°C, hydrogen peroxide was added, and the solution was stirred for 1 h. After workup and flash chromatography, the product **2** was obtained in 12% yield. In an effort to improve the yield, we applied the same procedure but with a higher temperature for the first two steps (100 and 180°C respectively); this new protocol resulted in a 52% yield after purification. Next we examined the effect of adding the $ZnCl_2$ at the first step in order to keep the flask closed throughout all steps in the synthesis; this change increased the yield to 57%. Finally, we found that replacing the $ZnCl_2$ with a 30% mol of Zn precluded the need for a constant flux of nitrogen to evacuate the hydrogen chloride that formed during the reaction, as hydrogen chloride reacts with zinc to form the $ZnCl_2$ catalyst *in situ*; this change did not affect the results.

Having determined the best methodology, we sought to synthesize various 6-(alkylamine)-6H-dibenz[c,e][1,2]oxaphosphinine-6-oxides (**2**) by changing diethylamine to other primary and secondary aliphatic amines; the results are presented in Figure 1. The use of secondary cyclic amines allowed us to obtain the desired product in 48–54% yield (**2b**-**2d**). The steric effect of diisopropylamine was reflected in a decreased yield of 41% (**2e**), which was lower than that obtained with isopropylamine (47%, **2f**) or

butylamine (49%, **2g**). Use of cyclohexylamine also caused a decrease in the yield (43%, **2h**), whereas cyclopropylamine afforded the best yield (69%, **2i**). Finally, the reaction was successful even with (*S*)-methylbenzylamine (41, 2j). We believe that the key step is the nucleophilic substitution of the chloride in the CDOP intermediate by the amine, because the oxidation of the CDOP without the addition of the nucleophile affords DOPO in 85% yield after purification. In all cases we obtained 6-(biphenyl-2-yloxy)-6H-dibenz[c,e][1,2]oxaphosphinine-6-oxide **3** as a by-product in 7% yield; this species is formed by the SN of 2-phenylphenol in CDOP and subsequent oxidation.

In conclusion, we have developed a straightforward one-pot method for synthesizing 6-(alkylamine)-6H-dibenz[c,e][1,2]oxaphosphinine-6-oxides (**2**). We used the proposed method to obtain six new compounds in good yield, and demonstrated that it is a general method for obtaining primary and secondary alkylamine derivatives.

EXPERIMENTAL

All chemicals were purchased from commercial sources and were used without purification. Solvents were purified using standard laboratory techniques. Infrared spectra were recorded on a Perkin Elmer Spectrum RX1 spectrometer. ^{1}H, ^{13}C and ^{31}P NMR were performed on a Varian Unity Inova 300 spectrometer at 300, 75 and 120 MHz in CDCl3 using TMS as an internal standard. Mass spectra were recorded on a Leco Pegasus 4D in positive ESI mode.

General procedure for the synthesis of 6-(alkylamine)-6H-dibenz[c,e][1,2]oxaphosphinine-6-oxides **2**.

1.3 mmol of 2-phenylphenol and 25 mg of Zn (30% mol) were placed in a flask with a magnetic stirrer under an inert atmosphere, and then 1.4 mmol of phosphorus trichloride was added via a cannula. The reaction mixture was heated at 100°C for 4 h with stirring, after which the temperature was raised to 180°C and the stirring was continued for 3 h. The reaction mixture was then cooled to R.T. and a solution of 1.9 mmol of the aliphatic amine in 10 mL of toluene was added via a cannula, and the mixture was stirred 3 h. After this period the reaction was cooled to 0°C and 0.4 mL of 30% hydrogen peroxide solution was added dropwise and the mixture was stirred for 1 h. The mixture was then extracted with brine (3 x 5 mL) and the organic phase was dried with anhydrous sodium sulfate and filtered, after which the solvent was evaporated. The crude product was purified by flash chromatography using Hex/AcOEt (1:1).

6-(Pyrrolidin-1-Yl)-6H-Dibenzo[C,E][1,2]Oxaphosphinine 6-Oxide (2b).

^{31}P NMR (120 MHz, $CDCl_3$) δ: 13.0. **^{1}H NMR (300 MHz, $CDCl_3$) δ:** 1.86 – 1.91 (q. *J*= 3.2 Hz, 4H), 3.16 – 3.33 (m, 4H) 7.20 – 8.02 (m, 8H). **^{13}C NMR (75 MHz, $CDCl_3$) δ:** 150 .4 (d, *J*= 7.4 Hz), 137.1 (d, *J*=7.0 Hz), 132.6 (d, *J*= 2.4 Hz), 130.2 (s), 129.74 (d, *J*= 9.1 Hz), 128.2 (d, *J*= 14.4 Hz), 124.9 (d, *J*= 1.0 Hz), 124.6 (d, 164.1 Hz), 124.1 (s), 123.7 (d, *J*= 11.3 Hz), 122.1 (d, *J*= 11.6 Hz), 120.5 (d, *J*= 6.3 Hz), 46.8 (d, *J*= 4.9 Hz), 26.5 (d, *J*= 8.7 Hz). **HRMS (ESI^+):** m/z calcd for $C_{16}H_{16}NO_2P$ [M+]:285.0919, found: 285.0897.

SUPLEMENTARY DATA

Full experimental detail, 1H, 13C and HRMS data for the new compounds can be found via the ‘‘Supplementary Content’’ section of this article’s webpage.

ACKNOWLEDGEMENTS

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Scheme 1. One-pot synthesis of 6-(alkylamine)-6H-dibenz[c,e][1,2]oxaphosphinine-6-oxides **2**.

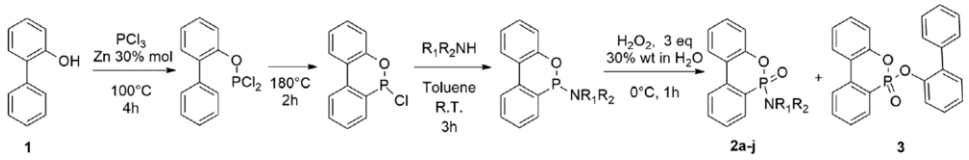

Figure 1. 6-(alkylamine)-6H-dibenz[c,e][1,2]oxaphosphinine-6-oxides **2** obtained. **2a**, **2c**, **2g** and **2j**,[6, 8] were previously reported, all other compounds are new.