A study of coupling reaction to synthesize diphenylmethane derivatives

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1. Introduction

Diphenylmethane scaffold is found in various compounds of commercial importance in pharmaceutics [1] and fine chemical industries [2,3]. These compounds serve as important intermediates in the synthesis of new drug candidates [4,5], adhesives and epoxy resins [6,7], preserves in perfumes and as solvent in pressure sensitive reaction [8]. The diphenylmethane derivatives are also added to improve the thermal stability of polyesters [9] and lubricating properties of jet fuels [10]. However, there are some diphenylmethane derivatives, which have been isolated from natural sources and possess significant bioactivities. A class of brominated diphenylmethane derivatives 1 which has been isolated from green alga Avrainvillea nigriicons and possessed antibiotic activity against several human pathogens [11] (Figure 1). While, recently a new diphenylmethane derivative 2 has been isolated from the bioactive mixture of Periploca sepium which, exhibited activity against autoimmune diseases, especially for the treatment of rheumatoid in traditional Chinese medicines [12] (Figure 1).

The diverse applications of diphenylmethane derivatives make them interesting target for synthetic chemists. In literature, usually Friedel-Craft reactions that including acylation or alkylation were employed to prepare diphenylmethane derivatives.

1.1. Halogenating reactions

1.1.1. Phosphorus tribromide

Halogenating agents

Thionyl chloride

Benzyl alcohol

Bis-(benzyloxy)-5-methoxyphenyl)methane.

It has been found that the coupling reaction is strongly influenced by the electronic effects and number of the substituents on the phenyl ring. The resultant compound, bis(2,4-bis(benzyloxy)-5-methoxyphenyl)methane, was obtained in excellent yield (83-85%) and completely characterize with different spectroscopic techniques.

1.2. Alkylation

However, in acylation the incorporation of formaldehyde group between two benzene rings is found tedious; while in alkylation the synthesis of benzyl chloride is sometime found inconvenient and low yielding [13,14].
Table 1. Coupling reaction attempts with mono-substituted benzyl alcohol.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzy alcohol</th>
<th>Reaction conditions</th>
<th>Halogenated product</th>
<th>Diphenylmethane derivative</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(3)</td>
<td>SOCl₂, CH₂Cl₂, 0°C to R.T., 24 hr</td>
<td>No product</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>MeO</td>
<td>SOCl₂, CH₂Cl₂, 0°C to R.T., 24 hr</td>
<td>No product</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>O₂N</td>
<td>SOCl₂, CH₂Cl₂, 0°C to R.T., 24 hr</td>
<td>No product</td>
<td></td>
</tr>
</tbody>
</table>

Also, both of the Friedel-Crafts reaction necessarily required Lewis acids such as AlCl₃, FeCl₃, or ZnCl₂, as pre-catalyst. These acid catalysts offer toxicity and various environmental hazardous effects [15,16]. So, in the loop of diphenyl methane analogues synthesis, we wish to report a unique cross-coupling approach to synthesize the diphenyl methane derivatives from benzyl alcohol derivatives.

2. Experimental

2.1. Materials

All the benzyl chlorides, halogenating agents and solvents were purchased from different available commercial sources. Silica gel column chromatography was performed with silica gel 60 as the stationary phase with different analytical grade solvents i.e. EtOAc, hexane, petroleum ether. Chromatograms were visualized by UV at 254 and 365 nm.

2.2. Instrumentation


2.3. Synthesis of diphenylmethane derivative, bis(2,4-bis(benzylxoy)-5-methoxyphenyl)methane (12)

Method 1: The solution of thionylchloride (SOCl₂) [0.01 mL, 0.21 mmole] in CH₂Cl₂ was added dropwise to the cold (0°C) stirring solution of 2,4-bis(benzylxoy)-5-methoxyphenyl)methanol 11 [100 mg, 0.28 mmoles] in CH₂Cl₂. The resulting mixture was stirred for 45 min at 0°C, at which the solution was poured into ice water and extracted with dichloromethane (CH₂Cl₂). All the separated organic layers were combined, dried over MgSO₄ and then subsequently evaporated dried the crude product by column chromatography to get the product 12 in 85% yield. With phosphorus tribromide (PBr₃), same protocol was used to afford the diphenylmethane derivative 12 in 83% yield.

Method 2: Methane sulphonl chloride (4.9 mL, 50.4 mmols) was added dropwise to a solution of 2,4-bis(benzylxoy)-5-methoxyphenyl)methanol 11 [3.6 g, 12.6 mmoles] and Et₂N (7 mL, 50.4 mmol) in THF (50 mL) at 0°C. The resulting mixture was then stirred overnight at room temperature. The reaction was quenched with water and extracted with the Et₂O and washed with brine, purified by column chromatography to get pure product 12 (3.9 g) in 83% yield. The structures of resultant compound 12 were confirmed with NMR spectroscopy, mass spectrometry and X-ray crystallography.

Bis(2,4-bis(benzylxoy)-5-methoxyphenyl)methane (12): Color: White crystals. 1H NMR (300 MHz, CDCl₃, δ, ppm): 7.49-7.10 (m, 20H, ArH), 6.52 (x, 2H, ArH), 6.50 (s, 2H, ArH), 5.02 (s, 4H, 2(CH₂)); 4.80 (s, 4H, 2(CH₂)); 3.80 (s, 2H, ClH); 3.50 (s, 6H, OCH₃). 13C NMR (75 MHz, CDCl₃, δ, ppm): 150.4 (C), 146.7 (C), 143.9 (C), 137.4 (C), 128.5 (CH), 127.7 (CH), 127.3 (CH), 122.6 (C), 115.5 (CH), 102.3 (CH), 71.7 (CH₃ x 2), 71.0 (CH₃ x 2), 56.5 (OCH₃ x 2), 29.7 (CH₃). MS-El (m/z, %): 652.2 (100), 653.29 (M⁺, 41).

3. Results and discussion

The cross-coupling reaction to prepare the diphenyl methane analogues from readily available benzyl alcohol derivatives were studied with various halogenating agents such SOCl₂, PBr₃ and MeSO₂Cl. Initially, the benzyl alcohol was treated with thionyl chloride to produce the desired diphenyl methane. Unfortunately, the reaction proved to be unsuccessful and no desired product 6 was obtained. Further, the mono substituted benzyl alcohol derivatives 4 and 5, with electron denoting group (4′-OMe) and electron withdrawing group (4′-NO₂) were treated with thionyl chloride to see whether the electronic effect of substituents electronic affect the synthesis of corresponding diphenylmethane derivatives. However in both cases, only the corresponding halogenated products 7 and 8 were obtained (Table 1).

Further in this study, a tri-substituted brominated benzyl alcohol derivative 9 was then treated with thionyl chloride to get corresponding diphenylmethane derivative 10, which has close structural similarity with precursor of dibromo diphenyl methane derivative 2. We have observed that even in this case the reaction resulted in only the corresponding benzyl chloride product (Scheme 1). Though, we had obtained surprising results when we applied the above mentioned reaction conditions (SOCl₂, CH₂Cl₂) with another tri-substituted benzyl alcohol derivative 11 having all the substitutes of electron denoting nature. The cross coupling type reaction proceeded smoothly and region-selectively to give the desired diphenyl methane derivative 12 in excellent yield (83-85%). The resultant compound 12 has a close structural similarity with dimethoxydiphenylmethane derivative 2. This suggested that a highly substituted phenyl ring with electro donating groups is necessarily required for such type of cross coupling reactions. The chemical method was further elaborated with other halogenating reagents such as PBr₃ and MeSO₂Cl, which also afforded the same product 12 (Scheme 1).

A plausible mechanism of this reaction has also been layout in the following Scheme 2. The first step in mechanism showed the chlorination of the benzyl alcohol derivative 11 to corresponding benzyl chloride 13 which then tautomerase with its more stable carbocation specie 14 due to the effect of different electron donating substituents on the phenyl ring. Next the nucleophilic attack of the phenyl ring of benzyl alcohol 11 formed the diphenylmethane intermediate 15, which rapidly released a molecule of formaldehyde to retain the aromaticity.
The resultant coupling product 12 was obtained in excellent yield (83-85%). The structure of the diphenylmethane analogue 12 was characterized with different analytical techniques which are including 1H NMR, 13C NMR spectroscopy and mass spectrometry. The structure was further confirmed by X-ray crystallography (Figure 2, Table 2-4).

Table 2. Crystal data and structure refinement for compound 12.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SOCl₂, 0 °C, 45 min.</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>PbBr₂, DCM, 0 °C, 45 min.</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>MeSO₂Cl, Et₂N, DCM, 0 °C to R.T. overnight</td>
<td>83</td>
</tr>
</tbody>
</table>

Scheme 1

4. Conclusion

We have prepared a highly substituted diphenylmethane derivative 12, which has close structural similarity with the nature product 2, via a simple coupling reaction. The reaction with substituted benzyl alcohol 11 was optimized with three different types of halogenated reagents. The percentage yield of the desired diphenylmethane derivative 12 with each reaction condition was found excellent (83-85%). Altogether, the chemical method is rapid and useful to exceed the substituted diphenylmethane derivative 12 of biological importance and intermediates as well in the chemical industry.
**Supplementary material**

CCDC-1001414 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

**References**


**Acknowledgement**

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### Table 4. Bond angles for compound 12

<table>
<thead>
<tr>
<th>Atom-Atom-Atom</th>
<th>Angle (°)</th>
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</thead>
<tbody>
<tr>
<td>C15-C14-C13</td>
<td>120.6(3)</td>
</tr>
<tr>
<td>C15-C14-C16</td>
<td>120.5(3)</td>
</tr>
<tr>
<td>C15-C16-C14</td>
<td>120.6(3)</td>
</tr>
<tr>
<td>C15-C16-C17</td>
<td>119.3(3)</td>
</tr>
<tr>
<td>C15-C17-C16</td>
<td>120.5(3)</td>
</tr>
<tr>
<td>C15-C17-C18</td>
<td>119.3(3)</td>
</tr>
<tr>
<td>C15-C18-C17</td>
<td>120.5(3)</td>
</tr>
<tr>
<td>C15-C18-C19</td>
<td>119.3(3)</td>
</tr>
<tr>
<td>C15-C19-C18</td>
<td>120.5(3)</td>
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<tr>
<td>C15-C19-C20</td>
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<td>C15-C21-C20</td>
<td>120.5(3)</td>
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</tbody>
</table>

### Scheme 2

![Scheme 2](image-url)