European Journal of Chemistry 5 (3) (2014) 513-516

European Journal of Chemistry

Journal homepage: www.eurjchem.com

A study of coupling reaction to synthesize diphenylmethane derivatives

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ARTICLE INFORMATION

DOI: 10.5155/eurjchem.5.3.513-516.1086

Received: 28 April 2014
Received in revised form: 26 May 2014
Accepted: 01 June 2014
Online: 30 September 2014

KEYWORDS

Benzyl alcohol
Thionyl chloride
Coupling reaction
Halogenating agents
Phosphorus tribromide
Diphenylmethane derivative

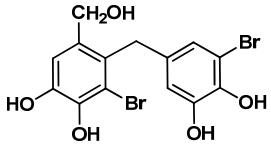
ABSTRACT

The class of compounds having diphenylmethane framework occupy a distinct place in natural bioactive compounds and also serve as useful intermediates in various commercially important synthetic molecules. Conventionally, Friedel-Craft type reactions were used to synthesize such diphenylmethane derivatives. However, herein we report a unique approach in which, two benzyl alcohol molecules were coupled in the presence of different halogenating agents ($SOCl_2$, PBr_3 and $MeSO_2Cl$) to afford the desired diphenylmethane derivative, *bis*(2,4-*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.

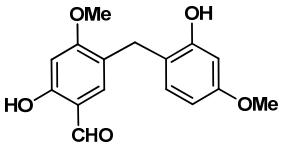
1. Introduction

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 diphenyl methane 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 diphenyl methane derivatives **1** which has been isolated from green alga *Avrainvillea nigrlcans* 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.



Dibromo diphenylmethane derivative 1



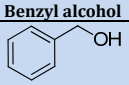
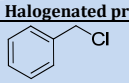
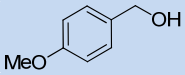
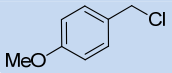
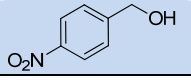
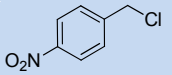
Dimethoxy diphenylmethane derivative 2

Figure 1. Naturally occurring diphenylmethane derivatives **1** and **2**.

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].

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
http://dx.doi.org/10.5155/eurjchem.5.3.513-516.1086

Table 1. Coupling reaction attempts with mono-substituted benzyl alcohol.

Entry	Benzyl alcohol		Reaction conditions	Halogenated product		Diphenylmethane derivative
1		(3)	$SOCl_2$, CH_2Cl_2, 0 °C to R.T., 24 hr		(6)	No product
2		(4)	$SOCl_2$, CH_2Cl_2, 0 °C to R.T., 24 hr		(7)	No product
3		(5)	$SOCl_2$, CH_2Cl_2, 0 °C to R.T., 24 hr		(8)	No product

Also, both of the Friedel-Crafts reaction necessarily required Lewis acids such as $AlCl_3$, $FeCl_3$, or $ZnCl_2$, 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

NMR spectra were obtained on Advance Bruker AM 300 and 400 MHz. Single crystal X-ray diffraction data: Diffractometer: Nonius KappaCCD area detector (ϕ scans and ω scans to fill asymmetric unit). Cell determination: DirAx [17], Data collection: COLLECT data collection software [18]. Data reduction and cell refinement: Denzo [19]. Absorption correction: Sheldrick, G. M. SADABS-Bruker Nonius area detector scaling and absorption correction-V2.10 Structure solution: SHELXS97 [20]. Structure refinement: SHELXL97 (G. M. Sheldrick (1997), University of Göttingen, Germany). Graphics: Cameron-A Molecular Graphics Package [21]. Special details: All hydrogen atoms were placed in idealized positions and refined using a riding model.

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

Method 1: The solution of thionylchloride ($SOCl_2$) (0.01 mL, 0.21 mmole) in CH_2Cl_2 was added dropwise to the cold (0 °C) stirring solution of 2,4-*bis*(benzyloxy)-5-methoxyphenyl) methanol **11** (100 mg, 0.28 mmoles) in CH_2Cl_2. The resulting mixture was stirred for 45 min at 0 °C, at which the solution was poured into ice water and extracted with dichloromethane (CH_2Cl_2). All the separated organic layers were combined, dried over $MgSO_4$ and then subsequently evaporated dried the crude product by column chromatography to get the product **12** in 85 % yield. With phosphoroustribromide (PBr_3), same protocol was used to afford the diphenylmethane derivative **12** in 83% yield.

Method 2: Methane sulphonyl chloride (4.9 mL, 50.4 mmols) was added dropwise to a solution of 2,4-*bis*(benzy loxy)-5-methoxyphenyl)methanol **11** (3.6 g, 12.6 mmoles) and Et_3N (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 Et_2O 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*(benzyloxy)-5-methoxyphenyl)methane (**12**): Color: White crystals. ^{1}H NMR (300 MHz, $CHCl_3$, δ, ppm): 7.49-7.10 (m, 20H, ArH), 6.52 (s, 2H, ArH), 6.50 (s, 2H, ArH), 5.02 (s, 4H, 2(CH_2)), 4.80 (s, 4H, 2(CH_2)), 3.80 (s, 2H, CH_2), 3.50 (s, 6H, $(OCH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 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 (CH_2 x 2), 71.0 (CH_2 x 2), 56.5 (OCH_3 x 2), 29.7 (CH_2). MS-EI (*m/z*, %): 652.2 (100), 653.29 (M^+, 41).

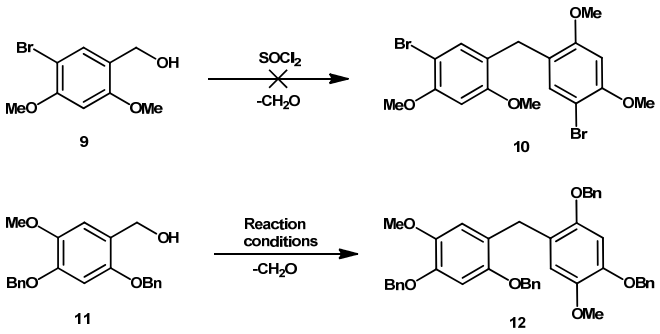
3. Results and discussion

The cross-coupling reaction to prepare the diphenyl methane analogues from readily available benzyl alcohol derivatives were studied with various halogenating agents such $SOCl_2$, PBr_3 and $MeSO_2Cl$. 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′-NO_2) 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 ($SOCl_2$, CH_2Cl_2) 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 dimethoxydip henylmethane derivative **2**. This suggested that a highly substituted phenyl ring with electro denoting groups is necessarily required for such type of cross coupling reactions. The chemical method was further elaborated with other halogenating reagents such as PBr_3 and $MeSO_2Cl$, 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 tautomerize with its more stable carbocation specie **14** due to the effect of different electron denoting 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.



Entry	Reaction conditions	% Yield
1	$SOCl_2$, 0 °C, 45 min.	85
2	PBr_3, DCM, 0 °C, 45 min.	83
3	$MeSO_2Cl$, Et_3N, DCM, 0 °C to R.T. overnight	83

Scheme 1

The resultant coupling product **12** was obtained in excellent yield (83-85%). The structure of the diphenyl methane analogue **12** was characterized with different analytical techniques which are including ^1H NMR, ^{13}C 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**.

Empirical formula	$C_{43}H_{40}O_6$
Formula weight	652.75
Temperature, K	120(2)
Crystal system	Monoclinic
Wavelength, Å	0.71073
Space group	$P2_1/n$
a, Å	15.7508(2)
b, Å	9.7835(2)
c, Å	21.9581(4)
α, °	90.00
β, °	92.4920(10)
γ, °	90.00
Volume/Å^3	3380.50(10)
Z	4
ρ_{calc}, mg/mm^3	1.283
m, mm^{-1}	0.085
F(000)	1384.0
Crystal size, mm^3	0.3 × 0.03 × 0.03
Crystal	Needle, Colourless
2Θ range for data collection	6.04 to 54.96°
Index ranges	$-20 \le h \le 20$, $-12 \le k \le 11$, $-28 \le l \le 28$
Reflections collected	41608
Completeness to θ = 27.48°	99.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9975 and 0.9651
Refinement method	Full-matrix least-squares on F^2
Independent reflections	7748[R(int) = 0.0720]
Data/restraints/parameters	7748/0/444
Goodness-of-fit on F^2	1.054
Final R indexes [I≥2σ (I)]	R_1 = 0.0820, wR_2 = 0.1560
Final R indexes [all data]	R_1 = 0.1246, wR_2 = 0.1796
Largest diff. peak/hole , e Å^{-3}	0.413/-0.290

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 excess the substituted diphenylmethane derivative **12** of biological importance and intermediates as well in the chemical industry.

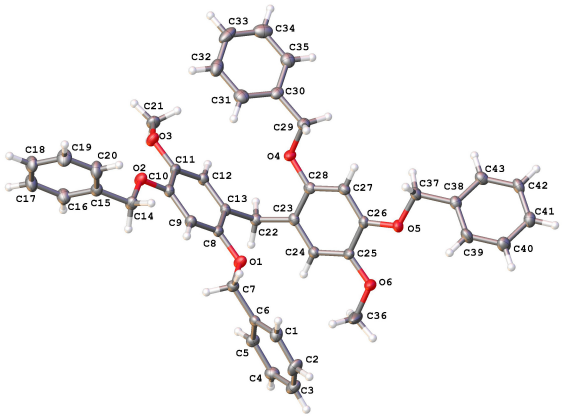
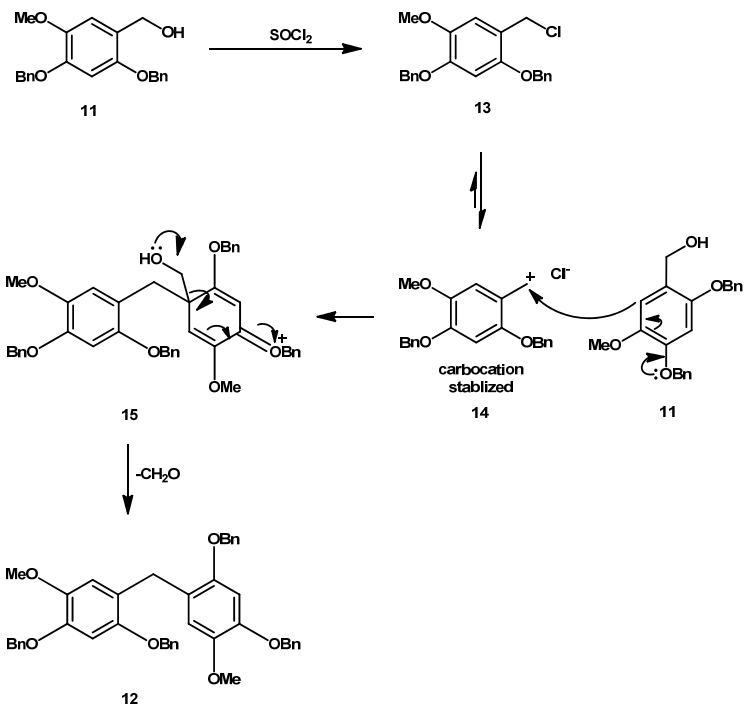


Figure 2. Crystal structure of compound **12**.

Table 3. Bond lengths for compound **12**.

Atom-Atom	Length, Å	Atom-Atom	Length, Å
C1-C2	1.386(4)	C22-C23	1.522(4)
C1-C6	1.382(4)	C23-C24	1.394(4)
C2-C3	1.380(5)	C23-C28	1.388(4)
C3-C4	1.393(4)	C24-C25	1.388(4)
C4-C5	1.386(4)	C25-C26	1.400(4)
C5-C6	1.393(4)	C25-O6	1.373(3)
C6-C7	1.506(4)	C26-C27	1.388(4)
C7-O1	1.429(3)	C26-O5	1.368(3)
C8-C9	1.392(4)	C27-C28	1.395(4)
C8-C13	1.395(4)	C28-O4	1.384(3)
C8-O1	1.381(3)	C29-C30	1.502(4)
C9-C10	1.392(4)	C29-O4	1.439(3)
C10-C11	1.400(4)	C30-C31	1.384(4)
C10-O2	1.376(3)	C30-C35	1.387(4)
C11-C12	1.376(4)	C31-C32	1.384(5)
C11-O3	1.382(3)	C32-C33	1.372(5)
C12-C13	1.391(4)	C33-C34	1.384(5)
C13-C22	1.515(4)	C34-C35	1.402(5)
C14-C15	1.503(4)	C36-O6	1.423(4)
C14-O2	1.441(3)	C37-C38	1.500(4)
C15-C16	1.387(4)	C37-O5	1.437(3)
C15-C20	1.378(4)	C38-C39	1.395(4)
C16-C17	1.384(4)	C38-C43	1.388(4)
C17-C18	1.383(5)	C39-C40	1.387(4)
C18-C19	1.376(5)	C40-C41	1.388(4)
C19-C20	1.388(4)	C41-C42	1.386(4)
C21-O3	1.425(3)	C42-C43	1.386(4)



Scheme 2

Table 4. Bond angles for compound **12**.

Atom-Atom-Atom	Angle, °	Atom-Atom-Atom	Angle, °
C6-C1-C2	120.6(3)	C25-C24-C23	122.0(3)
C3-C2-C1	120.5(3)	C24-C25-C26	119.2(2)
C2-C3-C4	119.5(3)	O6-C25-C24	125.3(2)
C5-C4-C3	119.9(3)	O6-C25-C26	115.5(2)
C4-C5-C6	120.6(3)	C27-C26-C25	119.5(3)
C1-C6-C5	119.0(3)	O5-C26-C25	115.7(2)
C1-C6-C7	120.9(3)	O5-C26-C27	124.8(2)
C5-C6-C7	120.1(3)	C26-C27-C28	120.2(3)
O1-C7-C6	108.2(2)	C23-C28-C27	121.1(3)
C9-C8-C13	121.2(2)	O4-C28-C23	116.7(2)
O1-C8-C9	123.5(2)	O4-C28-C27	122.2(2)
O1-C8-C13	115.4(2)	O4-C29-C30	107.6(2)
C8-C9-C10	119.8(3)	C31-C30-C29	121.0(3)
C9-C10-C11	119.5(3)	C35-C30-C29	120.0(3)
O2-C10-C9	124.5(2)	C35-C30-C31	119.0(3)
O2-C10-C11	116.0(2)	C32-C31C30	120.8(3)
C12-C11-C10	119.5(2)	C33-C32-C31	120.3(3)
C12-C11-O3	124.7(2)	C32-C33-C34	120.0(3)
O3-C11-C10	115.7(2)	C33-C34-C35	119.8(3)
C11-C12-C13	122.1(3)	C30-C35-C34	120.1(3)
C8-C13-C22	121.2(2)	O5-C37-C38	107.4(2)
C12-C13-C8	117.8(2)	C39-C38-C37	121.0(2)
C12-C13-C22	121.1(2)	C43-C38-C37	120.1(3)
O2-C14-C15	108.5(2)	C43-C38-C39	118.9(3)
C16-C15-C14	120.1(3)	C40-C39-C38	120.3(3)
C20-C15-C14	121.3(3)	C41-C40-C39	120.4(3)
C20-C15-C16	118.6(3)	C42-C41-C40	119.5(3)
C17-C16-C15	120.6(3)	C41-C42-C43	120.2(3)
C18-C17-C16	120.2(3)	C38-C43-C42	120.8(3)
C19-C18-C17	119.5(3)	C8-O1-C7	117.7(2)
C18-C19-C20	120.1(3)	C10-O2-C14	116.2(2)
C15-C20-C19	121.0(3)	C11-O3-C21	116.2(2)
C13-C22-C23	115.2(2)	C28-O4-C29	116.5(2)
C24-C23-C22	119.5(2)	C26-O5-C37	118.2(2)
C28-C23-C22	122.6(2)	C25-O6-C36	116.2(2)
C28-C23-C24	117.9(2)		

Acknowledgement

We are thankful to Higher Education Commission of Pakistan for providing financial support of this project.

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, 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

[1]. Bastock, T. W.; Clark, J. H. Speciality Chemicals, Elsevier, London, 1991.
[2]. Khadilkar, B. M.; Borkar, S. D. *Chem. Technol. Biotechnol*. **1998**, *71*, 209-212.
[3]. Commandeur, R.; Berger, N.; Jay, P.; Kervennal, J. J. Eur. Pat. Appl. EP 0442 986, 1991.
[4]. Feng, X. E.; Zhao, W. Y.; Ban, S. R.; Zhao, C. X.; Li, Q. S.; Lin, W. H. *Int. J. Mol. Sci*. **2011**, *12*, 6104-6115.
[5]. Balaydın, H. T.; Gılcin, I.; Menzek, A.; Goksu, S.; Sahin, E. *J. Enzyme Inhib. Med. Chem.* **2010**, *25*, 685-695.
[6]. Akutsu, M. A. C.; Otsuka, T. A. C. EP 1808223 B1, 2012.
[7]. Amano, S.; Tomita, H., US 5679730 A, 1997.
[8]. Sato, A.; Yida, Y.; Shimizi, I., DE-OS, 2 210 133, 1972.
[9]. Stewart, M. I.; Carlson, O. K., US Patent, 3 593 640, 1967.
[10]. Leus, A. M., US Patent, 3 529 944, 1967.
[11]. Colon, M.; Guevara, P.; Gerwick, W. H.; Ballantine, D. *J. Nat. Prod.* **1987**, *50*, 368-374.
[12]. Wang, L.; Yin, Z. Q.; Shen, W. B.; Zhang, Q. W.; Ye, W. C. *Helv. Chim. Acta* **2007**, *90*, 1581-1585.
[13]. Ku, Y. Y.; Patel, R. R.; Sawick, D. P. *Tetrahedron Lett.* **1996**, *37*, 1949-1952.
[14]. Wei, Q.; Luo, Y.; Zhou, M.; Tao, F.; Zhang, G. *Synth. Commun*. **2005**, *35*, 835-843.
[15]. Yin, D.; Li, C.; Tao, L.; Yu, N.; Hu, S.; Yin, D. *J. Mol. Catal. A: Chem*. **2006**, *245*, 260-265.
[16]. Olah, G. A. Friedel-Crafts Chemistry: Wiley, New York, 1973.
[17]. Duisenberg, A. J. M. *J. Appl. Cryst.* **1992**, *25*, 92-96.
[18]. Hooft, R. COLLECT. Nonius BV, Delft, The Netherlands, 1998.
[19]. Otwinowski, Z.; Minor, W. Methods in Enzymology; In Macromolecular Crystallography, Part A; Jr, C. W. C., Sweet, R. M., Eds.; Academic Press: New York, 1997; vol. 276.
[20]. Sheldrick, G. M. *Acta Cryst. A* **1990**, *46*, 467- 473.
[21]. Watkin, D. M.; Pearce, L.; Prout, C. K. Chemical Crystallography Laboratory; University of Oxford, 1993.