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A simple, efficient and scalable synthesis of substituted bis-arylchloromethanes

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An efficient and scalable two-step synthesis of bis-arylchloromethanes, an important building block for the synthesis of biologically important aryl piperidine and piperazine derivatives, and its 4,4'-disubstituted analogues is described.

Keywords: Substituted bis-arylchloromethanes; scalable synthesis; biologically active compounds.

INTRODUCTION

Diphenylchloromethane and its halogen substituted analogues are important building blocks for the synthesis of aryl piperazine compounds which are important structural units for the synthesis of a variety of biological compounds [1-3]. This skeleton has also been established as a useful privileged scaffold for library synthesis and drug discovery applications. A number of diphenyl methyl piperazine derivatives are being used as pharmaceuticals for a range of different biological targets [4]. Similarly, the diphenylmethoxy skeleton is the key structural element of the widely employed anticholinergic, antihistaminic agents and dopamine reuptake inhibitors as well [5]. *Ebastine*, *benzatropine* and *vanoxerine* are the most relevant examples that constitute diphenylmethoxy as an integral unit (Figure 1).

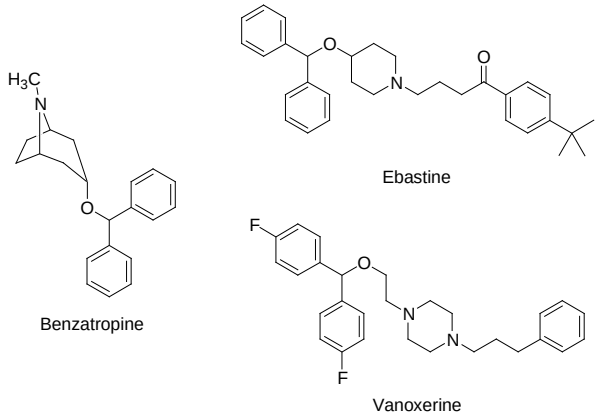

Fig. 1. Biologically important molecules possessing diarylmethane moieties

As a consequence, a number of synthetic methods have been reported for the synthesis of diphenylchloromethane and its derivatives. In particular, synthetic routes involving the use of transition metal reagents and catalysts have been described. Though a variety of synthetic protocols are reported in the literature, the use of toxic, expensive and air-sensitive aryl metal reagents and catalysts in presence of anhydrous solvents restrict their application on a practical scale. Further, cumbersome catalyst recovery and product contamination are additional drawbacks of these methodologies. Moreover, it is difficult to ensure robustness and reproducibility on kilogram scale using these reagents. Herein we report an efficient large-scale procedure for the synthesis of diphenylchloromethane and its derivatives.

In a two-step synthetic pathway, Scheme 1, benzophenone **1a-c** is reduced to benzhydryl **2a-c** using sodium borohydride, which on nucleophilic substitution with thionyl chloride, furnishes the dichlorophenylmethane **3a-c**.

EXPERIMENTAL

All raw materials were obtained from commercial suppliers and were used as received. Melting points were determined on a Buchi B-545 digital melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian-400 spectrometer using $CDCl_3$ as the solvent with TMS as the internal standard. The reaction was monitored and the purity of the compounds was analyzed using HPLC.

General procedures

Diarylmethanol (2a-c): To a cold solution of benzophenone **1a-c** in methanol (5 vol.) sodium borohydride (1 equiv.) was added and the mixture was stirred for 1 h at the same temperature. After complete consumption of the starting material (monitored by TLC), excess methanol was removed from the reaction mixture under reduced pressure. The reaction mixture was then quenched with water (5 vol.), extracted with ethyl acetate, dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated to dryness to obtain crude diarylmethanol **2a-c** which was used in the next step.

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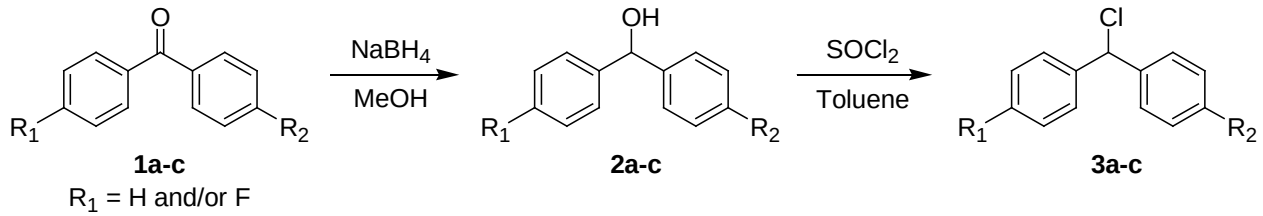

Scheme 1. Two-step synthesis of chlorodiphenylmethanes

Chlorodiarylmethane (3a-c): To a cold solution of diarylmethanol **2a-c** in toluene (5 vol.) thionyl chloride (1.25 equiv.) was slowly added and the mixture was stirred for 1 h at room temperature. After complete consumption of the starting material (monitored by TLC), the reaction mixture was poured into ice-cold water (10 vol.), extracted with ethyl acetate, dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness under reduced pressure to obtain pure chlorodiarylmethane **3a-c** as oil.

EXPERIMENTAL DATA

*Diphenylmethanol (**2a**)*[6]: Off white solid; yield 88.0 %; IR (ν cm^{-1}): 3337 (OH), 3061, 3028, 1960, 1894, 1813, 1599, 1493, 1451, 1348, 1268, 1178, 1019, 912, 852, 737, 700, 656, 602, 543; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (4H, d, *J* = 7.6 Hz), 7.34 (4H, dd, *J* = 14.8 and 7.6 Hz), 7.27 (2H, d, *J* = 7.2 Hz), 5.85 (1H, s, C*H*-OH), 2.21 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.8 (2C), 128.5 (4C), 127.6 (2C), 126.6 (4C), 76.2 (CH, *C*H-OH).

*Chlorodiphenylmethane (**3a**)*[6]: Colourless oil; yield 90.0 %; purity 98.0 % (area % by HPLC); IR (ν cm^{-1}): 3063, 3031, 1953, 1886, 1806, 1758, 1661, 1599, 1493, 1451, 1317, 1263, 1216, 1077, 1030, 1003, 918, 825, 748, 699, 627, 583, 504, 470; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41 (4H, d, *J* 7.6 Hz), 7.35 (4H, dd, *J* = 14.8 and 7.6 Hz), 7.28 (2H, d, *J* = 7.2 Hz), 6.1 (1H, s, C*H*-Cl); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.2 (2C), 128.7 (4C), 128.2 (2C), 127.9 (4C), 64.4 (C, *C*H-Cl).

*(4-Fluorophenyl)phenylmethanol (**2b**)* [7]: Viscous semisolid compound; yield 92.0 %; IR (ν cm^{-1}): 3328 (OH), 3029, 2891, 2649, 2023, 1958, 1901, 1817, 1772, 1603, 1510, 1450, 1416, 1338, 1231, 1178, 1098, 1020, 921, 851, 816, 728, 699, 650, 623, 563, 533, 501, 468; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.26 (7H, m), 7.01 (2H, dd, *J* = 17.6 and 8.8 Hz), 5.83 (1H, s, C*H*-OH), 2.21 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.4,160.9, 143.6, 139.6, 139.5, 128.6, 128.3, 128.2, 127.7, 126.4, 115.4, 115.2, 75.6 (CH, *C*H-OH).

*Chloro-(4-fluorophenyl)phenylmethane (**3b**)*[7]: Colorless oil; yield 91.0 %; purity 98.0 % (area % by HPLC); IR (ν cm^{-1}): 3033, 2934, 1954, 1894, 1870, 1764, 1604, 1508, 1452, 1414, 1299, 1230, 1160, 1099, 1076, 919, 848, 817, 791, 731, 699, 632, 609, 539; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.20 (7H, m), 7.02 (2H, dd, *J* = 17.2 and 8.4 Hz), 6.11 (1H, s, CH-Cl); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.6, 161.2, 140.9, 137.2, 129.7, 129.6, 128.7, 128.3, 127.8, 115.6, 115.4, 63.6 (C, *C*H-Cl).

*Bis-(4-fluorophenyl)methanol (**2c**)*[6,8]: Viscous semisolid compound; yield 95.0 %; IR (ν cm^{-1}): 3348 (OH), 3072, 2885, 1896, 1770, 1604, 1509, 1414, 1299, 1227, 1181, 1157, 1099, 1015, 835, 779, 598, 555, 497; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32 (4H, dd, *J* = 8.0 and 6.0 Hz), 7.03 (4H, dd, *J* = 17.2 and 8.8 Hz), 5.82 (1H, s, C*H*-OH), 2.20 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.4, 161.0, 139.39, 139.36, 128.2 (2C), 128.1 (2C), 115.5 (2C), 115.3 (2C, 74.9 (CH, *C*H-OH).

*Chlorobis-(4-fluorophenyl)methane (**3c**)*[6,8]: Colourless oil; yield 90.0 %; purity 98.0 % (area % by HPLC); IR (ν cm^{-1}): 3046, 2935, 2799, 2584, 2456, 2386, 2259, 2011, 1895, 1767, 1652, 1604, 1509, 1414, 1300, 1231, 1160, 1099, 1015, 941, 836, 776, 749, 687, 624, 572, 527; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 (4H, dd, *J* = 7.2 and 5.2 Hz), 7.02 (4H, dd, *J* = 17.2 and 9.6 Hz), 6.09 (1H, s, C*H*-Cl); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.6, 161.2, 136.85, 136.82, 129.58 (2C), 129.50 (2C), 115.67 (2C), 115.45 (2C), 62.8 (C, *C*H-Cl).

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ПРОСТА, ЕФЕКТИВНА И МАЩАБИРАНА СИНТЕЗА НА СУБСТИТУИРАНИ БИС-АРИЛ-ХЛОРОМЕТАНИ

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