

BF₃·OEt₂-Mediated Benzylation of Arenes and Heteroarenes with Benzyl Ether Derivatives

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Abstract

An efficient BF₃·Et₂O-promoted benzylation of arenes and heteroarenes with various benzyl ether derivatives has been developed. This method provided alternative access to valuable diarylmethane in good yields under mild conditions via an easy work-up procedure.

Keywords: Friedel-Crafts Alkylation, BF₃·Et₂O, Diarylmethane, Benzyl Ether Derivatives, Arenes

1. Introduction

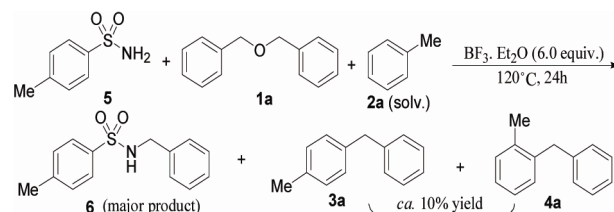
Diarylmethane motifs are an important class of aromatic building blocks which are found in various biologically active compounds such as anastrozole, papaverine, piritrexim, avrainvilleol, and beclobrate [1-5]. They are also used as key precursors in the synthesis of electroactive and photoactive oligomers and polymers [6,7]. Consequently, various methodologies for the alkylation of arenes and heteroarenes have been developed [8-10]. Among the various functionalization reactions of arenes, Friedel-Crafts alkylation (FCA) provides an efficient access to building a diarylmethane framework via the electrophilic addition of cationic species to aromatic compounds. Previous work about FCA has mainly centred on using alcohols [11-14], benzyl halides [15-18], aldehyde [19-21], carboxylic acid ester [22,23] or alkenes [24-26] as the alkylating agents in the presence of kinds of Brønsted acids, Lewis acids and transition metal salts [11-26], but there have not been many trials for the development of FCA with ethers as electrophilics possibly due to the stable ether bond. Nevertheless, recently Peris and Shiina group, *etc.* demonstrated that Ir-NHC complexes, SiCl₄/AgOTf and Hf(OTf)₄ *et al.* could efficiently catalyze alkylation of arenes using ethers as alkylating agents successively [24,27-30]. Considering the wide application of diarylmethane derivatives in the synthesis of biological molecules, the exploration of more economic catalysts for alkylation of arenes with ethers under mild conditions is desirable.

Recently, we have focused our attention on Lewis acid-catalyzed *N*-alkylation of sulfonamides using unactive

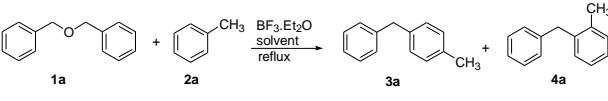
ethers as alkylating agents. During the period that we investigated the effect of various Lewis acids on the *N*-alkylation of 4-toluene sulfonamide **5** in toluene solvent, we found BF₃·Et₂O could enhance the formation of by-product diarylmethane **3a** and **4a** (around 10% yield) from the alkylation of toluene **2a** and benzyl ether **1a** (see **Scheme 1**), and further studies indicated that byproduct diarylmethane **3a** and **4a** did not form in the presence of other Lewis acids including AlCl₃, TiCl₄, Cu(OAc)₂·2H₂O, CdCl₂·2.5H₂O, ZrCl₄, MgO, *etc.* Herein, we reported our further studies about BF₃·Et₂O-promoted benzylation of arenes with benzyl ether derivatives.

2. Results and Discussions

Initially, the alkylation of toluene with dibenzyl ether was employed as a model reaction, optimization studies were carried out under different conditions, and the corresponding results were summarized in **Table 1**. As shown in **Table 1**, when the FCA of toluene (6.0 equiv.) with dibenzyl ether (0.5 mmol) was carried out using BF₃·Et₂O (3.0 equiv.) as promoter under refluxing condition in



Scheme 1. Lewis acid-promoted *N*-alkylation of sulfonamide and alkylation of toluene.

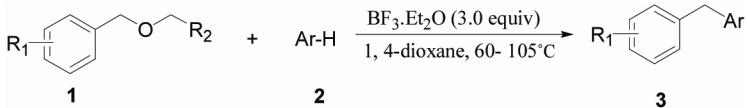
Table 1. Reaction conditions optimized for Friedel-Crafts benzylation of toluene.


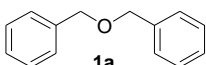

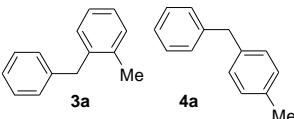
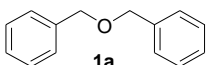

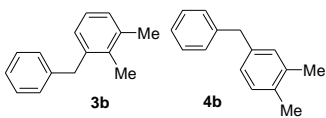
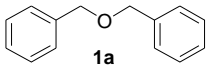
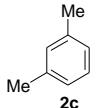
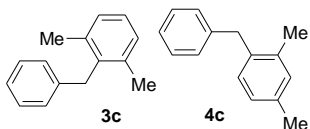
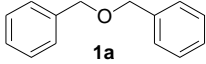
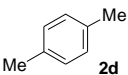
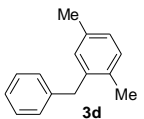
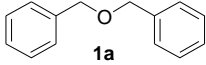
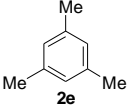
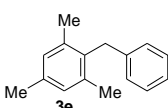
entry	toluene (equiv)	solvent	reaction time (h)	reaction temp. (°C)	yield ^b (%)
1	3	DMF	24	110	--
2	3	DMSO	24	150	--
3	3	CCl ₄	24	85	<10
4	3	CH ₃ CO ₂ Et	24	77	31
5	3	Acetone	24	56	18
6	3	CH ₃ CN	24	85	28
7	3	CHCl ₃	24	65	52
8	3	dioxane	24	110	68
9	3	TCE ^c	24	110	48
10	6	dioxane	24	110	75
11	8	dioxane	24	110	64
12	6	dioxane	24	90	57
13	6	dioxane	48	110	65
14	6	dioxane	24	140	63
15	6	dioxane	24	110	69 ^d
16	6	dioxane	24	110	72 ^e

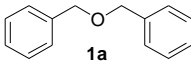
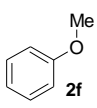
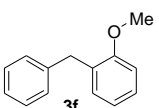
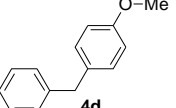
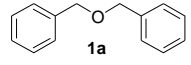

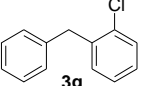
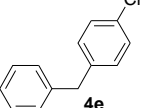
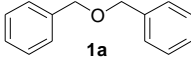

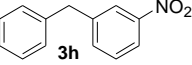
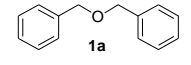

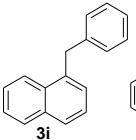
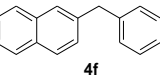
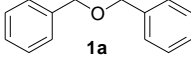
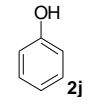
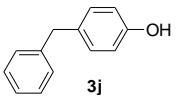
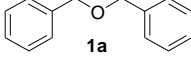

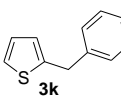
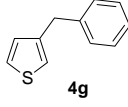
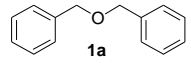

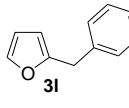
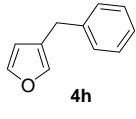
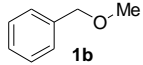

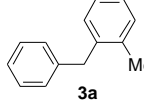
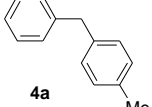
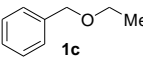

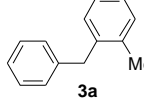
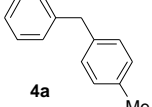
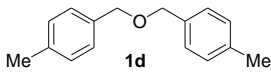

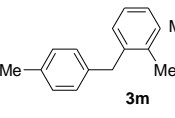
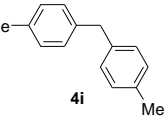
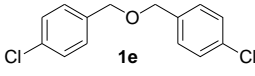

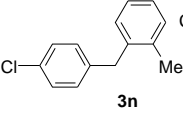
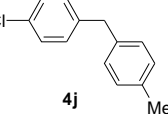
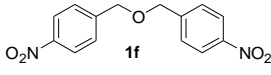

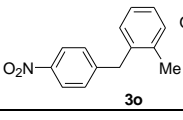
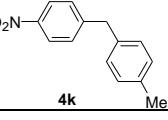
^aUnless otherwise noted, all the reactions were carried out under Ar atmosphere in sealed tube, benzyl ethers (0.5 mmol), BF₃·Et₂O (3.0 equiv), solvent (1.5 mL); ^bIsolated yield of isomers (**3a** and **4a**); ^cTCE: 1, 1, 2, 2-tetrachloroethane; ^d2.0 equiv of BF₃·Et₂O was used; ^e5.0 equiv of BF₃·Et₂O was used.

different solvents (1.5 mL) for 24 h, we found the nature of solvents had significant effect on this transformation (entries 1 - 9), among the solvents examined, 1,4-dioxane gave the best result (68% yield) (entry 8). The further optimized results indicated that the suitable substrate ratio (**2a/1a** = 12) could lead to the best yield (75%) (compare entries 8, 10 and 11), and lowering the reaction temperature to 90°C or increasing to 140°C resulted in a decreased yield due to incomplete reaction or tedious work-up, respectively (compare entries 10, 12 and 14). Finally, we investigated the effect of BF₃·Et₂O loading on the transformation, and found a decreased yield of diarylmethane was obtained at low promoter loading (2.0 equiv.) (compare entries 10 and 15), but higher promoter loading (5.0 equiv.) did not increase the yield of desired compound any further (compare entries 10 and 16).

With the optimized parameters in hand, we tested the general applicability of the BF₃·Et₂O-promoted FCA of arene with dibenzyl ether, by varying both the ether and the arene/heteroarene. As shown in **Table 2**, the benzyl ether alkylating reagents examined could be performed smoothly in moderate to good yields. Analysis of the efficiency about this transformation indicates that electronic effect governs the FCA system. The alkylation of dibenzyl ether with electron-rich aromatic compounds containing methyl, methoxy or hydroxyl group could occur

Table 2. BF₃·OEt₂-mediated Friedel-Crafts benzylation of different aromatic compound with benzyl ether derivatives^a.


entry	ethers	arenes	product ^b	yield ^c (%) (ratio: o/p)
1				74 (3:5)
2				73 (2:5)
3				80 (1:5)
4				71
5				78

6					49(1:5)
7					0
8					0
9					78 (4:1)
10					49
11					73 (2:1)
12					17 ^d (10:1)
13					68 (3:5)
14					66 (3:5)
15					68 (3:5)
16					76 (7:10)
17					53 ^c (7:10)

^aUnless otherwise noted, all reactions were carried out in sealed tube at 110°C under Ar atmosphere for 24 h, benzyl ethers (0.5 mmol), arenes (12.0 equiv), BF₃·Et₂O (3.0 equiv), 1, 4-dioxane used as solvent (1.5 mL); ^bAll products are known compounds and identified using ¹H NMR, LR-MS and IR; ^cIsolated yield and the ratio of the isomers were determined by ¹H NMR; ^dReaction temp.: 60°C, reaction time: 36 h; ^eReaction temp.: 150°C, reaction time: 42 h.

efficiently to afford diarylmethane in moderate to good yield (entries 1 - 6). On the contrary, benzyl ether derivatives with an electron-withdrawing group such as nitro gave lower yield of the corresponding alkylated products (compare entries 1 and 17). Even worse, if arenes had a chloride or nitro group, the FCA did not occur at all (entries 7 and 8). It is worth to note that $\text{BF}_3 \cdot \text{Et}_2\text{O}$ could also efficiently promote the benzylation of heteroarenes such as thiophene and furan to give corresponding diheteroaryl-methane (entries 11 and 12), but we found that the arene substrates containing oxygen hetero-atom gave low yield (17% - 49%) of alkylated product (entries 6, 10 and 12), this is possibly due to that the coordination of the ether oxygen or phenolic oxygen with B(III) decreased the electron density in the arene ring, and resulted in poor reactivity. It is more interesting that oxygen heteroatom-containing substrates such as **2f**, **2j** and **2l** gave poor yields of benzylated products, but better regioselectivity was observed (compare entries 1 and 6, 10 and 12), especially for substrate **2j**, 100% regioselectivity was achieved (entry 10).

3. Conclusions

In conclusion, we have demonstrated a $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -mediated benzylation of arenes and heteroarenes using benzyl ethers as the alkylating agents. Various ethers, arenes and heteroarenes were systematically studied, and low reactivity of oxygen-hetero atom-containing arenes was also observed. This method used inexpensive and commercially available $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as promoter, and provided complementary access to valuable diarylmethane under mild conditions.

4. General Experimental Information

Unless otherwise noted, all experiments were performed under Ar atmosphere in a sealed tube. All reagents were purchased from TCI, Acros or strem. Solvents were treated with 4Å molecular sieves or sodium and distilled prior to use. Purifications of reaction products were carried out by flash chromatography using silica gel (40 - 63 mm) from Qingdao Haiyang Chemical Co. Ltd. Infrared spectra (IR) were recorded on a Bruker TENSOR 27 FTIR spectrophotometer and are reported as wavelength numbers (cm^{-1}). ^1H NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) and coupling constants are reported as Hertz (Hz). Splitting patterns are designated as singlet (s), broad singlet (bs), doublet (d), triplet (t). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m). Low resolution mass spectra were recorded using GC-MS.

General Procedure

Benzyl ether derivatives (0.5 mmol), arenes or heteroarenes (6.0 mmol), $\text{BF}_3 \cdot \text{OEt}_2$ (3.0 equiv, 1.5 mmol) and 1,4-dioxane (1.5 mL) were combined in a pressure tube equipped with a stir bar. The mixture was heated to given temperature and stirred for the given time under Ar atmosphere. When the starting material has disappeared (monitored by TLC), the reaction mixture was treated with 10.0 mL of H_2O , filtrated and the corresponding filtrate was extracted with ethyl acetate (3×15 mL), the combined organic layers were concentrated, and the residue was purified by flash column chromatography (silica gel) to furnish target product. All products are known compounds and identified using ^1H NMR, LRMS and IR by comparison with previously reported data.

1-Benzyl-4-methylbenzene (**3a**) [31] and 1-benzyl-2-methylbenzene (**4a**) [32] (**3a/4a** = 5:3), liquid. **3a**: ^1H NMR (400 MHz, CDCl_3) δ : 7.24 (d, J = 6.1 Hz, 2 H), 7.04 (m, 7 H), 3.92 (s, 2H), 2.29 (s, 3 H); **4a**: ^1H NMR (400 MHz, CDCl_3) δ : 7.24 (d, J = 6.1 Hz, 2 H), 7.04 (m, 7 H), 3.97 (s, 2 H), 2.22 (s, 3 H); MS (ESI): m/z = 182.26 $[\text{M}]^+$; IR (KBr): 3294, 1720, 1597, 1443, 1332, 1210, 1167, 1027 cm^{-1} .

4-Benzyl-1,2-dimethylbenzene (**3b**) [33] and 1-benzyl-2,3-dimethylbenzene (**4b**) [34] (**3b/4b** = 5:2), liquid. **3b**: ^1H NMR (400 MHz, CDCl_3) δ : 7.28 - 7.22 (m, 2 H), 7.17 (d, J = 7.3 Hz, 2 H), 7.10 (d, J = 7.4 Hz, 1H), 7.08 - 7.00 (m, 1H), 6.99 - 6.94 (m, 1H), 6.91 (d, J = 7.6 Hz, 1 H), 3.90 (s, 2 H), 2.21 (s, 6H); **4b**: ^1H NMR (400 MHz, CDCl_3) δ : 7.28 - 7.22 (m, 2 H), 7.17 (d, J = 7.3 Hz, 2 H), 7.10 (d, J = 7.4 Hz, 1 H), 7.08 - 7.00 (m, 1 H), 6.99 - 6.94 (m, 1 H), 6.91 (d, J = 7.6 Hz, 1 H), 4.00 (s, 2 H), 2.27 (s, 3 H), 2.12 (s, 3 H); MS (ESI): m/z = 196.28 $[\text{M}]^+$; IR (KBr): 2923, 2854, 1817, 1764, 1727, 1588, 1481, 1095, 1026, 827, 741, 666, 567 cm^{-1} .

1-Benzyl-2,4-dimethylbenzene (**3c**) [35] and 2-benzyl-1,3-dimethylbenzene (**4c**) [33] (**3c/4c** = 5:1), liquid. **3c**: ^1H NMR (400 MHz, CDCl_3) δ : 7.29 - 6.90 (m, 7 H), 3.93 (s, 2 H), 2.29 (s, 3 H), 2.19 (s, 3 H); **4c**: ^1H NMR (400 MHz, CDCl_3) δ : 7.29 - 6.90 (m, 7 H), 4.04 (s, 2 H), 2.23 (s, 6 H); MS (ESI): m/z = 196.34 $[\text{M}]^+$, IR (KBr): 3119, 2921, 2853, 1742, 1696, 1516, 1462, 1355, 1229, 853, 634, 499 cm^{-1} .

2-Benzyl-1,4-dimethylbenzene (**3d**) [33], liquid. ^1H NMR (400 MHz, CDCl_3) δ : 7.25 (t, J = 7.4 Hz, 2 H), 7.14 (dd, J = 25.9, 8.2 Hz, 3 H), 7.04 (d, J = 7.9 Hz, 1 H), 6.97 - 6.90 (m, 2 H), 3.94 (s, 2 H), 2.28 (s, 3 H), 2.18 (s, 3 H); MS (ESI): m/z = 196.28 $[\text{M}]^+$, IR (KBr): 2924, 2856, 1734, 1504, 1458, 1377, 811, 735, 628 cm^{-1} .

2-Benzyl-1,3,5-trimethylbenzene (**3e**) [33], liquid. ^1H NMR (400 MHz, CDCl_3) δ : 7.20 (d, J = 7.8 Hz, 2 H), 7.14 (d, J = 7.1 Hz, 1 H), 7.00 (d, J = 7.5 Hz, 2 H), 6.88

(s, 2 H), 4.01 (s, 2 H), 2.28 (s, 3 H), 2.20 (s, 6 H); MS (ESI): $m/z = 210.31 [M]^+$, IR (KBr): 2923, 2856, 1640, 1515, 1457, 1385, 1319, 1257, 1097, 852, 691, 591 cm^{-1} .

1-Benzyl-4-methoxybenzene (**3f**) [36] and 1-benzyl-2-methoxybenzene (**4d**) [15] (**3f/4d** = 5:1), liquid. **3f**: ^1H NMR (400 MHz, CDCl_3) δ : 7.30 - 7.14 (m, 6 H), 7.08 (dd, $J = 16.4, 7.5$ Hz, 1 H), 6.88 - 6.80 (m, 2 H), 3.92 (s, 2 H), 3.77 (s, 3 H); **4d**: ^1H NMR (400 MHz, CDCl_3) δ : 7.30 - 7.14 (m, 6 H), 7.08 (dd, $J = 16.4, 7.5$ Hz, 1 H), 6.88 - 6.80 (m, 2 H), 3.97 (s, 2 H), 3.80 (s, 3 H); MS (ESI): $m/z = 198.26 [M]^+$, IR (KBr): 3459, 2924, 2856, 1726, 1599, 1459, 1384, 1248, 1101, 1033, 740, 547 cm^{-1} .

2-Benzyl-naphthalene (**3i**) [37] and 1-benzyl-naphthalene (**4f**)¹⁴ (**3i/4f** = 3:1), liquid. **3i**: ^1H NMR (400 MHz, CDCl_3) δ : 7.76 (dd, $J = 13.3, 7.8$ Hz, 3 H), 7.28 - 7.13 (m, 9 H), 4.12 (s, 2 H); **4f**: ^1H NMR (400 MHz, CDCl_3) δ : 7.99 - 7.96 (m, 2 H), 7.85 - 7.84 (m, 2 H), 7.44 - 7.37 (m, 8 H), 4.43 (s, 2 H); MS (ESI): $m/z = 218.29 [M]^+$; IR (KBr): 3054, 2922, 2855, 1812, 1724, 1596, 1496, 1446, 1388, 1263, 1076, 856, 786, 738, 706, 590, 513 cm^{-1} .

4-Benzylphenol (**3j**) [38], liquid. **3j**: ^1H NMR (400 MHz, CDCl_3) δ : 7.31 - 7.25 (m, 2 H), 7.24 - 7.17 (m, 3 H), 7.12 (dd, $J = 11.5, 4.5$ Hz, 2 H), 6.91 - 6.85 (m, 1 H), 6.75 (d, $J = 8.2$ Hz, 1 H), 4.75 (s, 1 H), 3.98 (s, 2 H); MS (ESI): $m/z = 184.23 [M]^+$, IR (KBr): 3678, 3029, 2890, 2824, 1746, 1700, 1496, 1333, 844, 746 cm^{-1} .

2-Benzylthiophene (**3k**) [39] and 3-benzylthiophene (**4g**)¹⁸ (**3k/4g** = 2:1), liquid. **3k**: ^1H NMR (400 MHz, CDCl_3) δ : 7.34 - 7.10 (m, 6 H), 6.90 (d, $J = 0.8$ Hz, 2 H), 4.14 (s, 2 H); **4g**: ^1H NMR (400 MHz, CDCl_3) δ : 7.34 - 7.10 (m, 6 H), 6.90 (d, $J = 0.8$ Hz, 2 H), 3.97 (s, 2 H); MS (ESI): $m/z = 174.29 [M]^+$; IR (KBr): 2923, 2855, 1739, 1639, 1458, 1384, 1264, 1203, 1264, 1203, 1096, 1030, 932, 741, 704, 558 cm^{-1} .

2-Benzylfuran (**3l**) [18] and 3-benzylfuran (**4h**) [39] (**3l/4h** = 10:1), liquid. **3l**: ^1H NMR (400 MHz, CDCl_3) δ : 7.30 (dd, $J = 12.0, 3.7$ Hz, 3 H), 7.23 (d, $J = 7.0$ Hz, 3 H), 6.28 (dd, $J = 2.9, 1.9$ Hz, 1 H), 6.00 (dd, $J = 3.1, 0.7$ Hz, 1 H), 3.96 (s, 2 H); **4h**: ^1H NMR (400 MHz, CDCl_3) δ : 7.30 (dd, $J = 12.0, 3.7$ Hz, 3 H), 7.23 (d, $J = 7.0$ Hz, 3 H), 6.28 (dd, $J = 2.9, 1.9$ Hz, 1 H), 6.00 (dd, $J = 3.1, 0.7$ Hz, 1 H), 3.77 (s, 2 H); MS (ESI): $m/z = 158.20 [M]^+$; IR (KBr): 2924, 2855, 1884, 1724, 1598, 1456, 1385, 1263, 1096, 1027, 932, 740, 556 cm^{-1} .

di-*p*-Tolylmethane (**3m**) [40] and *o*-tolyl(*p*-tolyl)methane (**4i**) [19] (**3m/4i** = 5:3), liquid. **3m**: ^1H NMR (400 MHz, CDCl_3) δ : 7.17 - 6.95 (m, 8 H), 3.88 (s, 2 H), 2.29 (s, 6 H); **4i**: ^1H NMR (400 MHz, CDCl_3) δ : 7.17 - 6.95 (m, 8 H), 3.93 (s, 2 H), 2.29 (s, 3 H), 2.23 (s, 3 H); MS (ESI): $m/z = 196.29 [M]^+$, IR (KBr): 2924, 2857, 1732, 1597, 1456, 1382, 1263, 1104, 1034, 799, 739, 607 cm^{-1} .

1-(4-Chlorobenzyl)-4-methylbenzene (**3n**) [41] and 1-(4-chlorobenzyl)-2-methylbenzene (**4j**) [42], (**3n/4j** =

10:7), liquid. **3n**: ^1H NMR (400 MHz, CDCl_3) δ : 7.26 - 7.20 (m, 2 H), 7.15 (d, $J = 9.1$ Hz, 2 H), 7.13 - 7.00 (m, 4 H), 6.95 (d, $J = 8.6$ Hz, 1 H), 3.89 (s, 2 H), 2.31 (s, 3 H); **4j**: ^1H NMR (400 MHz, CDCl_3) δ : 7.26 - 7.20 (m, 2 H), 7.15 (d, $J = 9.1$ Hz, 2 H), 7.13 - 7.00 (m, 4 H), 3.93 (s, 2 H), 2.21 (s, 3 H); MS (ESI): $m/z = 216.70 [M]^+$; IR (KBr): 2923, 2856, 1885, 1811, 1720, 1660, 1593, 1454, 1384, 1261, 1096, 798, 739, 698, 541 cm^{-1} .

1-(4-Nitrobenzyl)-4-methylbenzene (**3o**) [43] and 1-(4-nitrobenzyl)-2-methylbenzene (**4k**) [43] (**3o/4k** = 10:7), liquid. **3o**: ^1H NMR (400 MHz, CDCl_3) δ : 8.13 (dd, $J = 8.2, 3.8$ Hz, 2 H), 7.33 (dd, $J = 8.5, 3.6$ Hz, 2 H), 7.26 (d, $J = 9.3$ Hz, 2 H), 7.23 - 7.16 (m, 2 H), 4.03 (s, 2 H), 2.33 (s, 3 H); **4k**: ^1H NMR (400 MHz, CDCl_3) δ : 8.13 (dd, $J = 8.2, 3.8$ Hz, 2 H), 7.33 (dd, $J = 8.5, 3.6$ Hz, 2 H), 7.26 (d, $J = 9.3$ Hz, 2 H), 7.23 - 7.16 (m, 2 H), 4.08 (s, 2 H), 2.21 (s, 3 H); MS (ESI): $m/z = 227.25 [M]^+$; IR (KBr): 3021, 2922, 2858, 1924, 1729, 1599, 1515, 1342, 1179, 1106, 1026, 854, 736, 540 cm^{-1} .

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6. References

- [1] M. G. Nordberg, K. Kolmodin, J. Aquist, S. F. Queemer and A. J. Hallberg, "Design, Synthesis, Computational Prediction, and Biological Evaluation of Ester Soft Drug as Inhibitors of Dihydrofolate Reductase from *Pneumocystis Carinii*," *Journal of Medicinal Chemistry*, Vol. 44, No. 15, 2001, pp. 2391-2402.
[doi:10.1021/jm010856u](https://doi.org/10.1021/jm010856u)
- [2] H. H. Sun, V. J. Paul and W. Fenical, "Avrainvilleol, a Brominated Diphenylmethane Derivative with Feeding Deterrent Properties from the Tropical Green Alga *Avrainvillea Longicaulis*," *Phytochemistry*, Vol. 22, No. 3, 1983, pp. 743-745.
[doi:10.1016/S0031-9422\(00\)86974-5](https://doi.org/10.1016/S0031-9422(00)86974-5)
- [3] H. Hoshina, K. Maekawa, K. Taie, T. Igarashi and T. Salurai, "A New Route to Papaverine Analogs via Photocyclization of Substituted N-Acyl- α -dehydrophenylalaninamides," *Heterocycles*, Vol. 60, 2003, pp. 1779-1786.
- [4] C. Manzoni, M. R. Lovati, A. Bonelli, G. Galli and C. R. Sirtori, "Differential Effects of Beclobrate on Lipid/Lipoprotein Distribution in Normal and Hypercholesterolemic Rats," *European Journal of Pharmacology*, Vol. 190, No. 1-2, 1990, pp. 39-49.
[doi:10.1016/0014-2999\(90\)94110-J](https://doi.org/10.1016/0014-2999(90)94110-J)

- [5] C. Rose, O. Vtoraya, A. Pluzanska, N. Davidson, M. Gershanovich, R. Thomas, S. Johnson, J. Caicedo, H. Gervasio, G. Manikhas, F. B. Ayed, S. B. Radoux, H. A. C. Ross and R. Lang, "An Open Randomised Trial of Second-Line Endocrine Therapy in Advanced Breast Cancer: Comparison of the Aromatase Inhibitors Letrozole and Anastrozole," *European Journal of Cancer*, Vol. 39, No. 16, 2003, pp. 2318-2327. [doi:10.1016/S0959-8049\(03\)00630-0](https://doi.org/10.1016/S0959-8049(03)00630-0)
- [6] V. B. Andela, "Functional Antagonism between NF- κ B and Nuclear Receptors: Implications in Carcinogenesis and Strategies for Optimal Cancer Chemopreventive Interventions," *Current Cancer Drug Targets*, Vol. 4, No. 4, 2004, pp. 337-344. [doi:10.2174/1568009043332952](https://doi.org/10.2174/1568009043332952)
- [7] M. S. Khan, M. R. A. Al-Mandhary, M. K. Al-Suti, B. Ahrens, M. F. Mahon, L. Male, P. R. Raithby, C. E. Boothby and A. Kohler, "Synthesis, Characterisation and Optical Spectroscopy of Diynes and Poly-Ynes Containing Derivatized Fluorenes in the Backbone," *Dalton Transaction*, Vol. 1, 2003, pp. 74-84. [doi:10.1039/b208963g](https://doi.org/10.1039/b208963g)
- [8] S. L. You, Q. Cai and M. Zeng, "Chiral Brønsted Acid Catalyzed Friedel-Crafts Alkylation Reactions," *Chemical Society Reviews*, Vol. 38, No. 8, 2009, pp. 2190-2201. [doi:10.1039/b817310a](https://doi.org/10.1039/b817310a)
- [9] H. M. Peng, L. X. Dai and S. L. You, "Enantioselective Palladium-Catalyzed Direct Alkylation and Olefination Reaction of Simple Arenes," *Angewandte Chemie International Edition*, Vol. 49, No. 34, 2010, pp. 5826-5828. [doi:10.1002/anie.201000799](https://doi.org/10.1002/anie.201000799)
- [10] S. Messaoudi, J. D. Brion and M. Alami, "Transition-Metal-Catalyzed Direct C-H Alkenylation, Alkynylation, Benzoylation, and Alkylation of (Hetero) Arenes," *European Journal of Organic Chemistry*, Vol. 2010, No. 34, 2010, pp. 6495-6516. [doi:10.1002/ejoc.201000928](https://doi.org/10.1002/ejoc.201000928)
- [11] C. Zhang, X. Gao, J. Zhang and X. Peng, "Fe/CuBr₂-Catalyzed Benzoylation of Arenes and Thiophenes with Benzyl Alcohols," *Synlett*, Vol. 2, 2010, pp. 261-265. [doi:10.1055/s-0029-1218571](https://doi.org/10.1055/s-0029-1218571)
- [12] W. Yao, P. Makowski, C. Giordano and F. Goettmann, "Synthesis of Early-Transition-Metal Carbide and Nitride Nanoparticles through the Urea Route and Their Use as Alkylation Catalysts," *Chemistry—A European Journal*, Vol. 15, No. 44, 2009, pp. 11999-12004. [doi:10.1002/chem.200901496](https://doi.org/10.1002/chem.200901496)
- [13] P. Makowski, R. Rothe, A. Thomas, M. Niederberger and F. Moettmann, "Chlorine Borrowing: An Efficient Method for an Easier Use of Alcohols as Alkylation Agents," *Green Chemistry*, Vol. 11, 2009, pp. 34-37.
- [14] F. Wang and W. Ueda, "High Catalytic Efficiency of Nanostructured Molybdenum Trioxide in the Benzoylation of Arenes and an Investigation of the Reaction Mechanism," *Chemistry—A European Journal*, Vol. 15, No. 3, 2009, pp. 742-753. [doi:10.1002/chem.200801153](https://doi.org/10.1002/chem.200801153)
- [15] M. Kitano, K. Nakajima, J. N. Kondo, S. Hayashi and M. Hara, "Protonated Titanate Nanotubes as Solid Acid Catalyst," *Journal of the American Chemical Society*, Vol. 132, No. 19, 2010, pp. 6622-6623. [doi:10.1021/ja100435w](https://doi.org/10.1021/ja100435w)
- [16] P. K. Thallapally, C. A. Fernandez, R. K. Motkuri, S. K. Nune, J. Liu and C. H. F. Peden, "Micro and Mesoporous Metal-Organic Frameworks for Catalysis Applications," *Dalton Transactions*, Vol. 39, No. 7, 2010, pp. 1692-1694. [doi:10.1039/b921118g](https://doi.org/10.1039/b921118g)
- [17] V. L. Budarin, J. H. Clark, R. Luque and D. Macquarrie, "Versatile Mesoporous Carbonaceous Materials for Acid Catalysis," *Chemical Communications*, Vol. 6, 2007, pp. 634-636. [doi:10.1039/b614537j](https://doi.org/10.1039/b614537j)
- [18] G. A. Sereda, "Alkylation on Graphite in the Absence of Lewis Acids," *Tetrahedron Letters*, Vol. 45, No. 39, 2004, pp. 7265-2667. [doi:10.1016/j.tetlet.2004.08.026](https://doi.org/10.1016/j.tetlet.2004.08.026)
- [19] Y. Hashimoto, K. Hirata, H. Kagoshima, N. Kihara, M. Hasegawa and K. Saigo, "Gallium Dichloride-Mediated Reductive Friedel-Crafts Reaction," *Tetrahedron*, Vol. 49, No. 27, 1993, pp. 5969-5978. [doi:10.1016/S0040-4020\(01\)87183-0](https://doi.org/10.1016/S0040-4020(01)87183-0)
- [20] J. M. Aizpurua, B. Lecea and C. Palomo, "Reduction of Carbonyl Compounds Promoted by Silicon Hydrides under the Influence of Trimethylsilyl-Based Reagents," *Canadian Journal of Chemistry*, Vol. 64, No. 12, 1986, pp. 2342-2347. [doi:10.1139/v86-386](https://doi.org/10.1139/v86-386)
- [21] T. Miyai, Y. Onishi and A. Baba, "Indium Trichloride Catalyzed Reductive Friedel-Crafts Alkylation of Aromatics Using Carbonyl Compounds," *Tetrahedron Letters*, Vol. 39, No. 35, 1998, pp. 6291-6294. [doi:10.1016/S0040-4039\(98\)01333-1](https://doi.org/10.1016/S0040-4039(98)01333-1)
- [22] K. Mertins, I. Iovel, J. Kischel, A. Zapf and M. Beller, "Transition-Metal-Catalyzed Benzoylation of Arenes and Heteroarenes," *Angewandte Chemie International Edition*, Vol. 44, 2005, pp. 238-242. [doi:10.1002/anie.200460666](https://doi.org/10.1002/anie.200460666)
- [23] M. Rueping, B. J. Nachtsheim and W. Ieawsuwan, "An Effective Bismuth-Catalyzed Benzoylation of Arenes and Heteroarenes," *Advanced Synthesis & Catalysis*, Vol. 348, No. 9, 2006, pp. 1033-1037. [doi:10.1002/adsc.200606068](https://doi.org/10.1002/adsc.200606068)
- [24] A. Prades, R. Corberan, M. Poyatos and E. Peris, "A Simple Catalyst for the Efficient Benzoylation of Arenes by Using Alcohols, Ethers, Styrenes, Aldehydes, or Ketones," *Chemistry—A European Journal*, Vol. 15, No. 18, 2009, pp. 4610-4613. [doi:10.1002/chem.200802740](https://doi.org/10.1002/chem.200802740)
- [25] Y. P. Xiao, X. Y. Liu and C. M. Che, "Highly Efficient Gold(III)-Catalyzed Intermolecular Hydroarylation of Unactivated Alkenes with Arenes under Mild Conditions," *Journal of Organometallic Chemistry*, Vol. 694, No. 4, 2009, pp. 494-501. [doi:10.1016/j.jorganchem.2008.07.035](https://doi.org/10.1016/j.jorganchem.2008.07.035)
- [26] K. M. Reddy, N. S. Babu, P. S. S. Prasad and N. Lingaiah, "Aluminium-Exchanged Tungstophosphoric Acid: An Efficient Catalyst for Intermolecular Hydroarylation of Vinyl Arenes," *Catalysis Communications*, Vol. 9, No. 15, 2008, pp. 2525-2531. [doi:10.1016/j.catcom.2008.07.007](https://doi.org/10.1016/j.catcom.2008.07.007)
- [27] I. Shiina and M. Suzuki, "The Catalytic Friedel-Crafts Alkylation Reaction of Aromatic Compounds with Benzyl or Allyl Silyl Ethers Using Cl₂Si(OTf)₂ or Hf(OTf)₄," *Tetrahedron Letters*, Vol. 43, No. 36, 2002, pp. 6391-

6394. doi:10.1016/S0040-4039(02)01376-X
- [28] S. A. Ardizzone, P. Beltrame and G. Zuretti, "Kinetics of the Reaction of Toluene with Benzyl Alcohol over Sulfated Zirconia," *Applied Catalysis A: General*, Vol. 314, No. 2, 2006, pp. 240-247. doi:10.1016/j.apcata.2006.08.026
- [29] J. R. Satam and R. V. Jayaram, "Liquid Phase Friedel-Crafts Benzoylation of Aromatics on a Polymer-Supported 12-Tungstophosphoric Acid Catalyst," *Catalysis Communications*, Vol. 9, No. 9, 2008, pp. 1937-1940. doi:10.1016/j.catcom.2008.03.018
- [30] B. Q. Wang, S. K. Xiang, Z. P. Sun, B. T. Guan, P. Hu, K. Q. Zhao and Z. J. Shi, "Benzoylation of Arenes through FeCl₃-Catalyzed Friedel-Crafts Reaction via C-O Activation of Benzyl Ether," *Tetrahedron Letters*, Vol. 49, No. 27, 2008, pp. 4310-4312. doi:10.1016/j.tetlet.2008.04.117
- [31] N. Christoph and M. Herbert, "Kinetics of the Solvolyses of Fluoro-Substituted Benzhydryl Derivatives: Reference Electrodes for the Development of a Comprehensive Nucleofugality Scale," *European Journal of Organic Chemistry*, Vol. 2010, No. 8, 2010, pp. 1435-1439. doi:10.1002/ejoc.200901400
- [32] K. Tobias, V. Katja and L. Torsten, "Regioselective Arene Functionalization: Simple Substitution of Carboxylate by Alkyl Groups," *Chemistry—A European Journal*, Vol. 15, No. 44, 2009, pp. 12082-12091. doi:10.1002/chem.200901774
- [33] H. B. Sun, B. Li, S. J. Chen, J. Li and R. M. Hua, "An Efficient Synthesis of Unsymmetrical Diarylmethanes from the Dehydration of Arenes with Benzyl Alcohols Using InCl₃·4H₂O/Acetylacetone Catalyst System," *Tetrahedron*, Vol. 63, No. 41, 2007, pp. 10185-10188. doi:10.1016/j.tet.2007.07.093
- [34] M. Kristin, L. Irina, K. Jette and Z. Alexander, "Gold-Catalyzed Benzoylation of Arenes and Heteroarenes," *Advanced Synthesis & Catalysis*, Vol. 348, No. 6, 2006, pp. 691-695. doi:10.1002/adsc.200505433
- [35] F. Alice, T. Amy and B. William, "Palladium-Catalyzed Cross-Coupling of B-Benzyl-9-Borabicyclo[3.3.1]nonane to Furnish Methylene-Linked Biaryls," *Organic Letters*, Vol. 7, No. 22, 2005, pp. 4975-4978. doi:10.1021/ol051929x
- [36] A. Muriel and G. Corinne, "Synthesis of Functionalised Diarylmethanes via a Cobalt-Catalysed Cross-Coupling of Arylzinc Species with Benzyl Chlorides," *Chemical Communications*, Vol. 40, 2008, pp. 5019-5021. doi:10.1039/b809626k
- [37] M. Kenichi, K. Takeo, S. Norio, K. Kozo, G. Takahiro and N. J. Yukinori, "Synthesis of Novel Silyl Enol Ethers from Chlorodimethyl(Naphthylphenylmethyl)silanes Having a Chiral Centre and a Ketone and Their Chirality Transfer Effects in Crossed-Aldol Reactions," *Journal of Chemical Research*, Vol. 2009, No. 1, 2009, pp. 46-51. doi:10.3184/030823409X393709
- [38] C. R. Chen, S. L. Zhou and H. M. Gau, "Extremely Efficient Cross-Coupling of Benzylic Halides with Aryltitanium Tris(isopropoxide) Catalyzed by Low Loadings of a Simple Palladium(II) Acetate/Tris(*p*-tolyl) phosphine System," *Advanced Synthesis & Catalysis*, Vol. 352, No. 10, 2010, pp. 1718-1727. doi:10.1002/adsc.201000311
- [39] H. Nicolas, "One-Pot Dual Substitutions of Bromobenzyl Chloride, 2-Chloromethyl-6-halogenoimidazo[1,2-*a*]pyridine and -[1,2-*b*]pyridazine by Suzuki-Miyaura Cross-Coupling Reactions," *European Journal of Organic Chemistry*, Vol. 2008, No. 28, 2008, pp. 4824-4827. doi:10.1002/adsc.201000311
- [40] Z. K. Yu, "Synthesis and Structural Characterization of Complexes Derived from Treatment of Gallium Trichloride with 3,5-Diphenylpyrazole," *Polyhedron*, Vol. 21, No. 11, 2002, pp. 1117-1123. doi:10.1016/S0277-5387(02)00931-2
- [41] T. Lloyd Fletcher and J. Blackwell, "Experiments in the Colchicine Field. VI. A Method for the Synthesis of Ring B¹," *Journal of the Chemical Society*, 1961, pp. 1400-1420.
- [42] J. R. Schmink and N. E. Leadbeater, "Palladium-Catalyzed Synthesis of Diarylmethanes: Exploitation of Carbanionic Leaving Groups," *Organic Letters*, Vol. 11, No. 12, 2009, pp. 2575-2578. doi:10.1021/ol900874z
- [43] T. Z. Nichele and A. L. Monteiro, "Synthesis of Diarylmethane Derivatives from Stille Cross-Coupling Reactions of Benzylic Halides," *Tetrahedron Letters*, Vol. 48, 2007, pp. 7472-7475.