

SUPPORTING INFORMATION

Developing benign syntheses using ion pairs via solvent-free mechanochemistry

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SUPPLEMENTARY INFORMATION (PAGES S1-S11)

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EXPERIMENTAL (MATERIALS AND METHODS)

General Remarks S_N2 reactions were carried out by mechanochemical milling in a SPEX8000M Mixer Mill at a frequency of 18 Hz using a stainless steel vial with a 3/16" stainless steel ball bearing. ¹H and ¹³C {¹H}NMR spectra were obtained on a Bruker Avance 400 MHz spectrometer, and all chemical shift values are reported in ppm on the δ scale. GC-MS data were obtained with a Hewlett-Packard 6890 series GC-MS with a Zebron ZB-5, 15 mm x 0.25 mm x 0.25 mm column. Mass spectral determinations were carried out using ESI as the ionization method. Flash column chromatography was performed using a Combiflash® Automated Flash Column Chromatography system with RediSep Rf Gold® high performance flash columns (fine spherical silica gel 20-40 μm). Deuterated chloroform was obtained from Cambridge Isotope Laboratories, Inc., Andover, MA, and used without further purification.

All bases, 4-chlorobenzyl chloride, and 4-bromobenzyl bromide were purchased from Acros Organics and phenol was purchased from Fischer Scientific; all were used without further purification. The para-substituted benzyl halides were used due to their solid physical properties.

Typical procedure for preparing 4-bromobenzylphenyl ether To a custom-made 2.0 x 0.5 inch stainless steel screw capped vial was added phenol (1.00 mmol, 0.0941 g), 4-bromobenzyl halide (1.00 mmol), a metal carbonate (1.00 mmol), and a "3/16" stainless steel ball bearing. A Teflon gasket was added and the vial sealed and placed in a Spex 8000 mixer mill. The reaction was shaken for 16 hours at 18 hertz. The crude reaction mixture was extracted with approximately 25 mL of ethyl acetate and water. The organic layer was dried over anhydrous magnesium sulfate and solvent evaporated under reduced pressure to afford a mixture of products. The O-alkylated product was separated from the C-alkylated products by flash column chromatography on silica gel using heptane/ethyl acetate as the eluent. ¹H-NMR and GC-MS were used to assess the purity of the target molecule. Percent conversion was determined by ¹H-NMR integration.

Typical procedure for preparing 4-chlorobenzylphenyl ether 4-chlorobenzyl chloride (mp 27-29 °C) was slightly heated and added dropwise (1.00 mmol, 0.161 g) to a custom-made 2.0 x 0.5 inch stainless steel screw capped vial followed by phenol (1.00 mmol, 0.0941 g), a metal carbonate (1.00 mmol), and a 3/16" stainless steel ball bearing. A Teflon gasket was added, and the vial sealed and placed in a Spex 8000 mixer mill. The reaction was shaken for 16 hours at 18 hertz. The crude reaction mixture was extracted with approximately 25 mL of ethyl acetate and water. The organic layer was dried over anhydrous magnesium sulfate and solvent evaporated under reduced pressure to afford a mixture of products. The O-alkylated product was separated from the C-alkylated products by flash column chromatography on silica gel using heptane/ethyl acetate as the eluent. ¹H-NMR and GC-MS were used to assess the purity of the target molecule. Percent conversion was determined by ¹H-NMR integration.

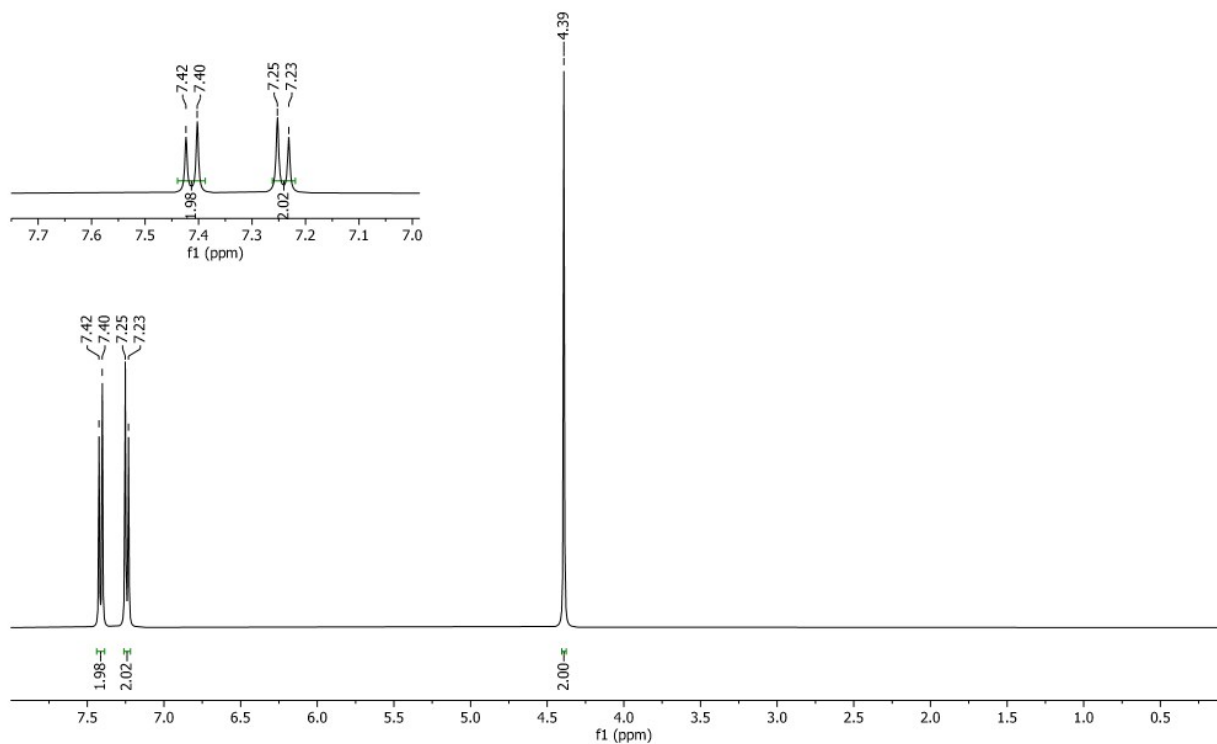
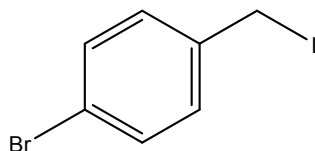
Typical procedure for preparing 4-bromobenzyl iodide

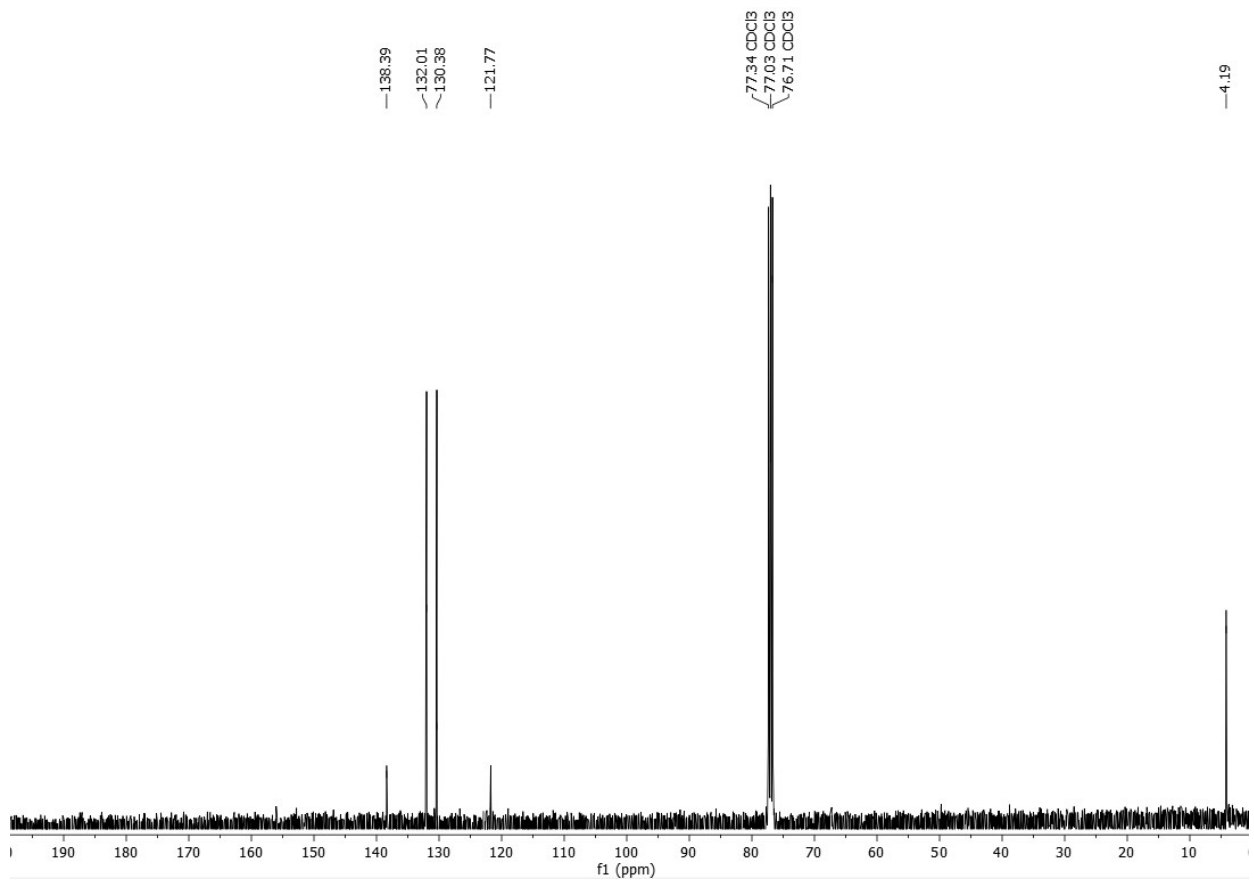
To a custom-made 2.0 x 0.5 inch stainless steel screw capped vial was added 4-bromobenzyl bromide (1.00 mmol, 0.250 g), sodium iodide (5.00 mmol, 0.750 g), 2 mL acetone, and three 3/16" stainless steel ball bearings. A Teflon gasket was added and the vial sealed and placed in a Spex 8000 mixer mill. The reaction was shaken for 5 hours at 18 hertz. The crude reaction mixture was gravity filtered and the solvent evaporated under reduced pressure. The organic product was then extracted with approximately 25 mL of ethyl acetate and water. The product was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to afford a quantitative amount of product. It should be noted the 4-bromobenzyl iodide should be used for these reactions within 24 hours of synthesis since it will begin to decompose in the presence of light.

Characterization data for 4-bromobenzyl iodide:

Acta Chim. Slov. 2015, 62, 775–783

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.42-7.40 (d, 2H, $J = 8$ Hz), 7.25-7.23 (d, 2H, $J = 8$ Hz), 4.39 (s, 2H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 4.19, 121.77, 130.38, 132.01, 138.39. **GCMS** calculated $[\text{M}]^+$ for $\text{C}_7\text{H}_6\text{BrI}$: 296.0, found: 295.9.

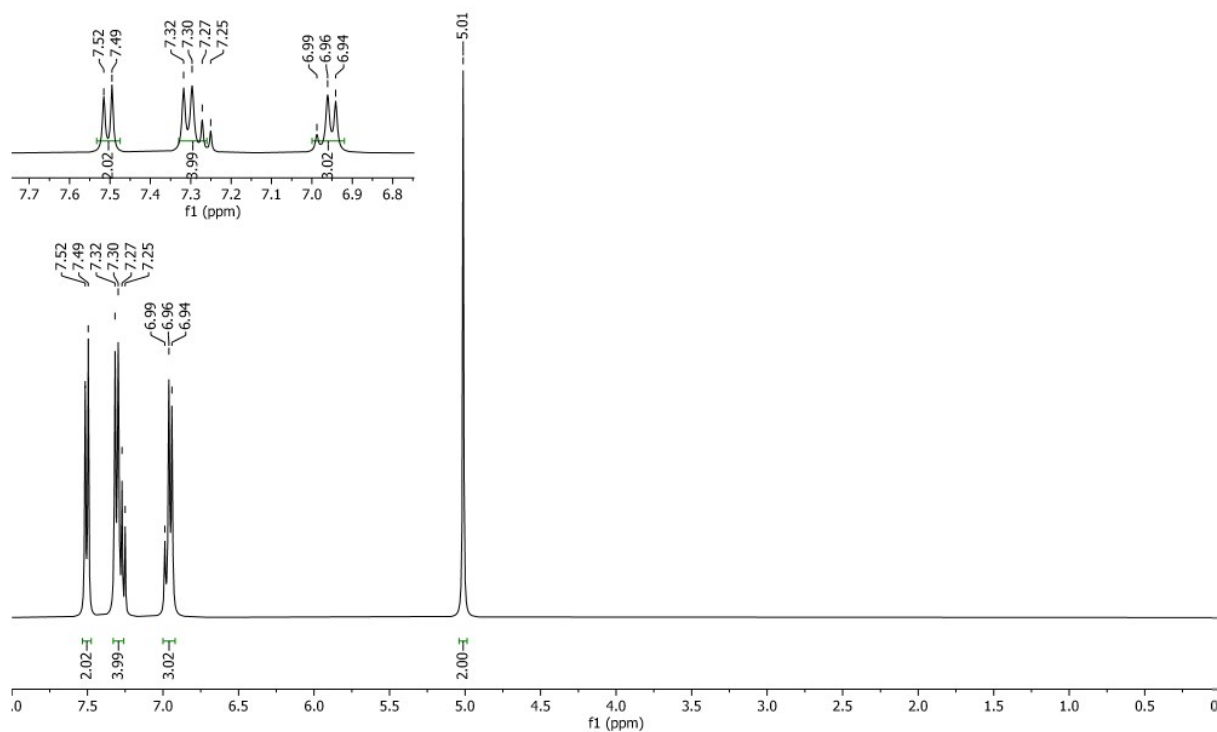
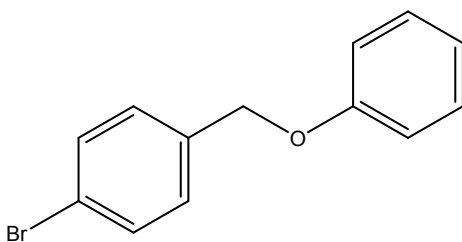


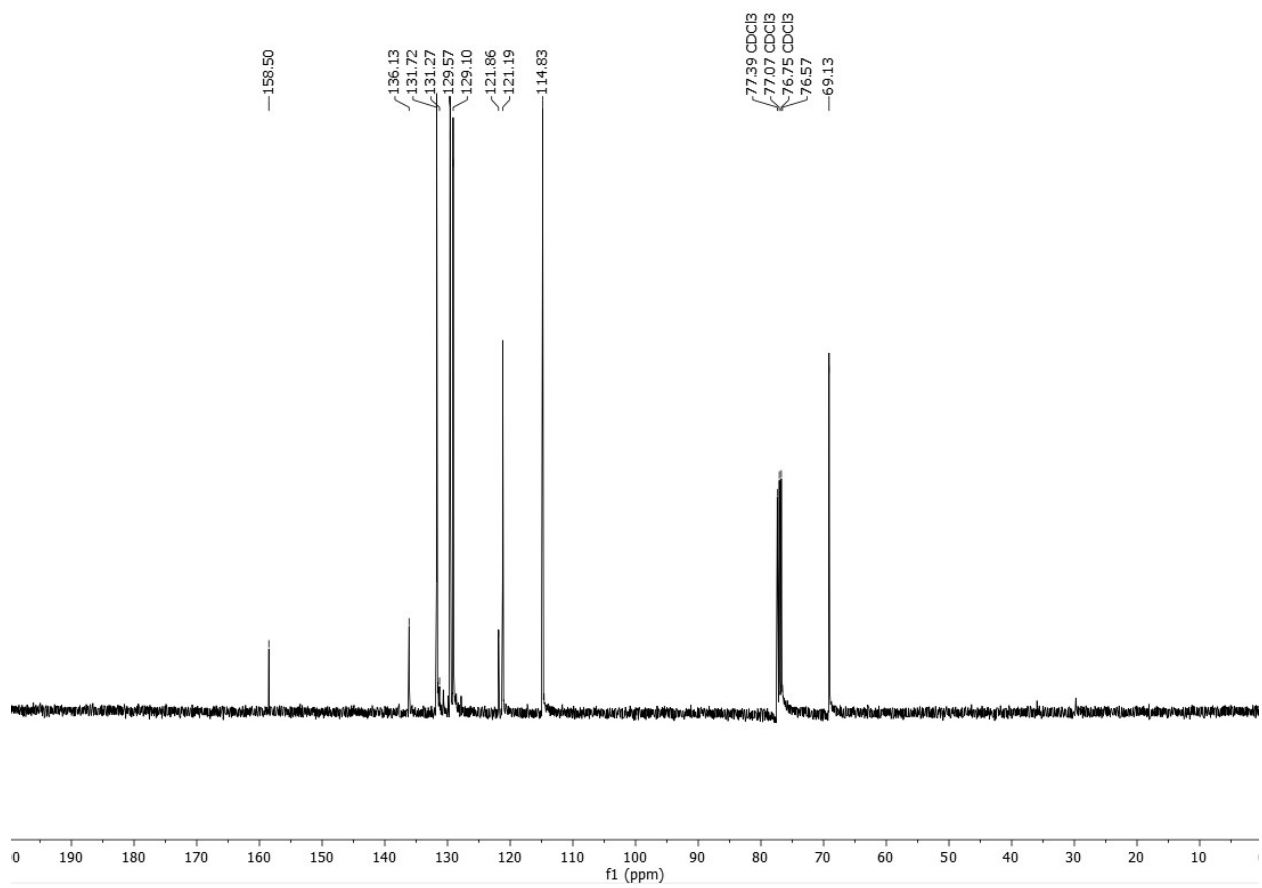


Characterization data for 1-Bromo-4-(phenoxyethyl)benzene

Chem. Commun., 2016,52, 1665-1668

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.52-7.49 (d, 2H, $J = 8$ Hz), 7.32-7.25 (m, 4H), 6.99-6.94 (m, 3H), 5.01 (s, 2H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 69.13, 114.83, 121.19, 121.86, 129.10, 129.57, 131.27, 131.72, 136.13, 158.50. **GCMS** calculated $[\text{M}]^+$ for $\text{C}_{13}\text{H}_{11}\text{BrO}$: 262.1, found: 262.0.

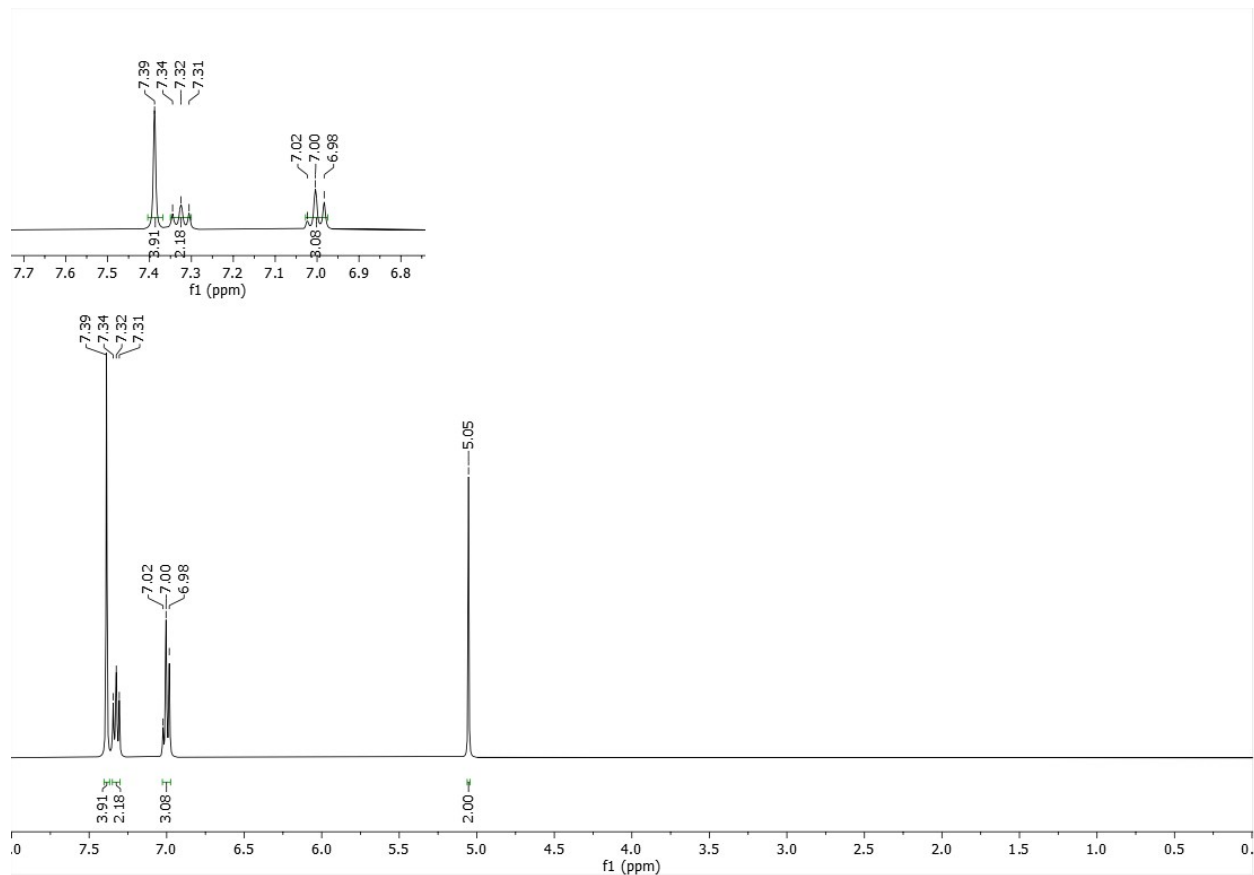


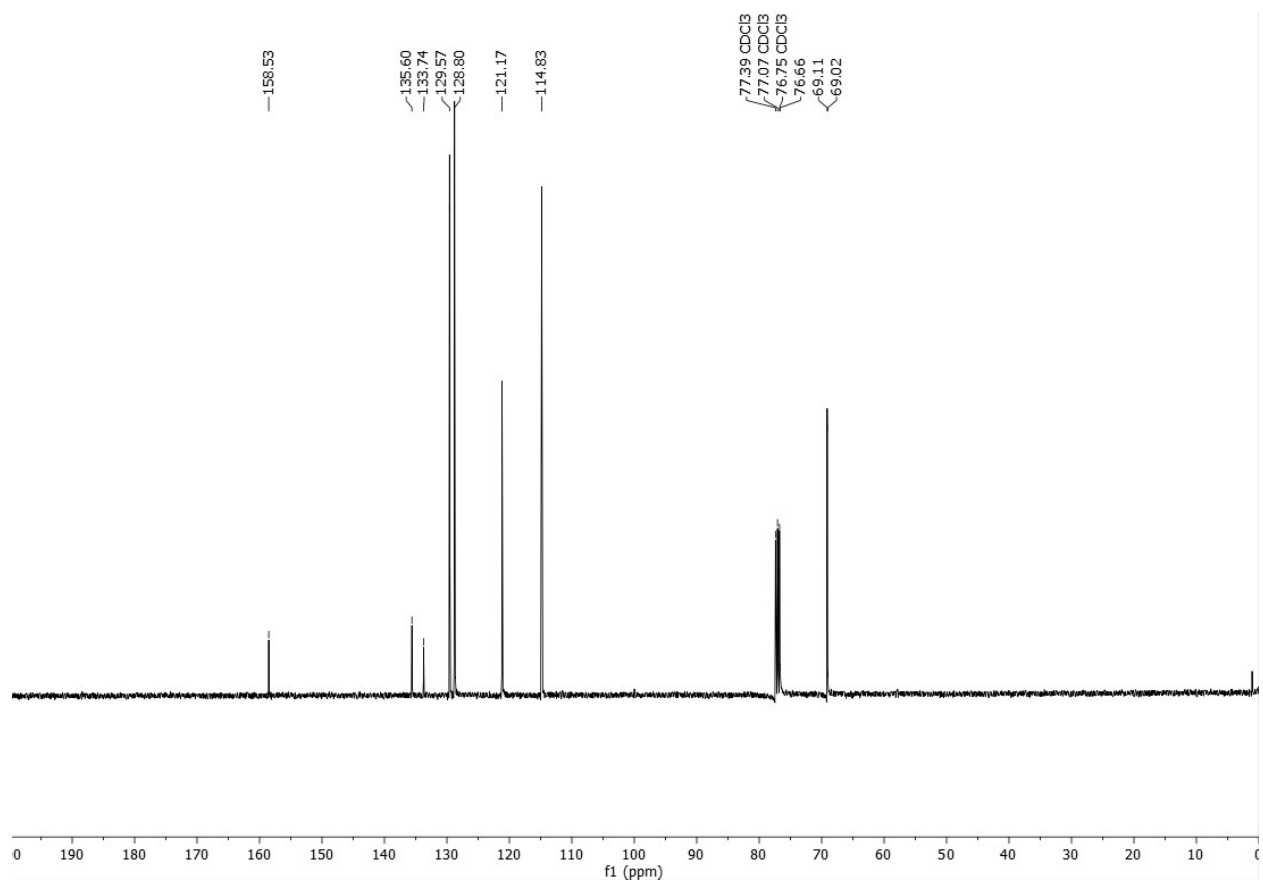


Characterization data for 1-Chloro-4-(phenoxy)methylbenzene

Chem. Commun., 2016, **52**, 1665-1668

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.39 (s, 4H) 7.34-7.31 (t, $J=7.9$ Hz, 2H), 7.02-6.98 (t, $J=8.4$ Hz, 3H), 5.05 (s, 2H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 69.12, 114.84, 121.18, 128.78, 128.81, 129.58, 133.74, 135.60, 158.53. **GCMS** calculated $[\text{M}]^+$ for $\text{C}_{13}\text{H}_{11}\text{ClO}$: 218.1, found: 218.1



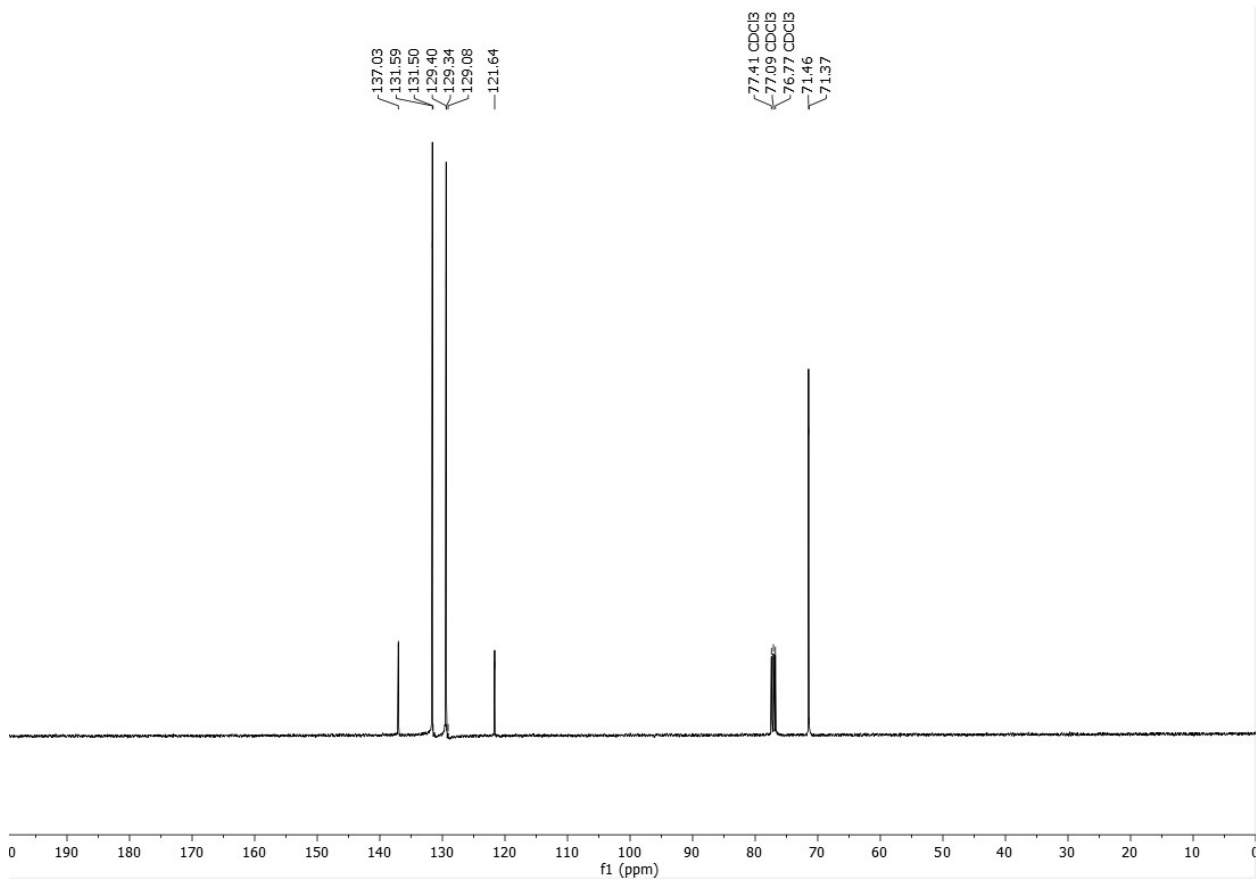


Characterization data for Bis (4-bromobenzyl ether)

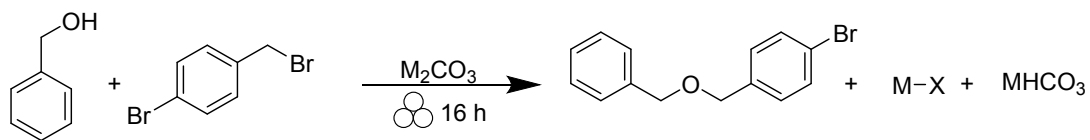
R. Savela, R. Leino, Synthesis 2015, 47, 1749-1760

$^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.48-7.46 (d, $J = 8.3$ Hz, 1H), 7.22-7.20 (d, $J = 8.3$ Hz, 1H), 4.48 (s, 1H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 71.46, 121.64, 129.08, 129.40, 131.59, 137.03. GCMS calculated $[\text{M}]^+$ for $\text{C}_{14}\text{H}_{12}\text{Br}_2$: 354.1, found: 356.0





EcoScale Calculations

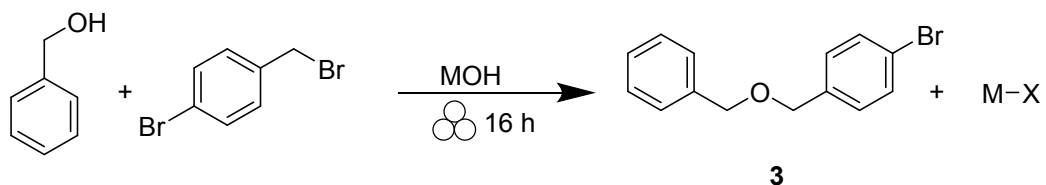


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	Solution		Mechanochemistry	
Item numbers	Item	Penalty	Item	Penalty
Yield / %	85	7.5	95	2.5
Price of reaction components	4-bromobenzyl bromide	0	4-bromobenzyl bromide	0
	Phenol	0	Phenol	0
	Potassium Carbonate	0	Cesium Carbonate	0
	DMF	0		
Safety	4-bromobenzyl bromide	0	4-bromobenzyl bromide	0
	Phenol	10	Phenol	10
	Cesium Carbonate	0	Cesium Carbonate	0
	DMF	5		
Technical Set-up	Common setup	0	Mechanochemistry	2
Temperature/time	Stirred room temp, 16 hr	0	None	0
Work up	liquid-liquid extraction	3	liquid-liquid extraction	3
	Column chromatography	10		
Total Penalty Points		35.5		17.5
EcoScale rating	64.5		82.5	
Overall Assessment	Acceptable		Excellent	

EcoScale Calculation

K. Van Aken, L. Strekowski and L. Patiny, *Beilstein J. Org. Chem.*, 2006, **2**, No. 3, doi:10.1186/1860-5397-1182-1183.



	Solution		Mechanochemistry	
Item numbers	Item	Penalty	Item	Penalty
Yield	90	5	88	6
Price of reaction components	4-bromobenzyl bromide	0	4-bromobenzyl bromide	0
	4-bromobenzyl alcohol	0		
	Sodium hydride	0	Cesium Hydroxide	0
	THF	0		
Safety	4-bromobenzyl bromide	0	4-bromobenzyl bromide	0
	4-bromobenzyl alcohol	0	4-bromobenzyl alcohol	0
	sodium hydride	5	Cesium hydroxide	0
	THF	5		
Technical Set-up	gas atmosphere	1	Mechanochemistry	2
Temperature/time	room temp overnight	1	None	0
Work up	liquid liquid extraction	3	liquid-liquid extraction	3
	column chromatography	10		
Total Penalty Points		30		11
EcoScale rating	70		89	
Overall Assessment	Acceptable		Excellent	