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of Reliable Methods  
for the Preparation  
of Organic Compounds

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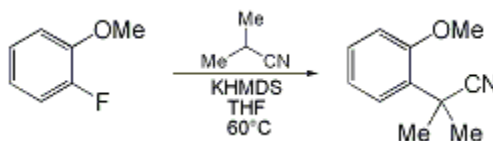
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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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## NUCLEOPHILIC AROMATIC SUBSTITUTION OF ARYL FLUORIDES BY SECONDARY NITRILES: PREPARATION OF 2-(2-METHOXYPHENYL)-2-METHYLPROPIONITRILE

[ Benzeneacetonitrile, 2-methoxy- $\alpha,\alpha$ -dimethyl- ]



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Checked by Li Dong and Marvin J. Miller.

### 1. Procedure

*2-(2-Methoxyphenyl)-2-methylpropionitrile*. A 300-mL, three-necked, round-bottomed flask equipped with a reflux condenser and a Teflon-coated magnetic stir bar is placed under a nitrogen atmosphere and charged with 2-fluoroanisole (10.00 g, 79.28 mmol) (Note 1), 100 mL of tetrahydrofuran (THF, Note 2) and potassium hexamethyldisilylamide (KHMDS, 23.72 g, 118.92 mmol) (Note 3). Isobutyronitrile (28.8 mL, 316.71 mmol) (Note 4) is added via syringe. The reaction mixture is heated to 60°C for 23 hr (Note 5). After the solution is cooled to room temperature, it is transferred to a 1000-mL separatory funnel containing 300 mL of methyl tert-butyl ether (Note 6) and 300 mL of 1 N hydrochloric acid (HCl). The organic layer is separated and washed successively with 300 mL of water and 200 mL of brine. The organic phase is dried over anhydrous magnesium sulfate (MgSO<sub>4</sub>), filtered, and concentrated to provide the desired product as a tan oil (13.75 g, 99%) (Notes 7, 8 and 9).

### 2. Notes

1. 2-Fluoroanisole was purchased from Aldrich Chemical Co., Inc., and used without further purification.
2. Anhydrous tetrahydrofuran was purchased from Aldrich Chemical Co., Inc., in a Sure/Seal™ bottle.
3. Potassium hexamethyldisilylamide was purchased from Aldrich Chemical Co., Inc., and used without further purification. The solid was weighed on a balance without special protection from air.
4. Isobutyronitrile was purchased from Aldrich Chemical Co., Inc., and used without further purification.
5. The reaction can be monitored by HPLC (Hewlett-Packard 1100 HPLC, Kromasil C18 column (4.6 × 150 mm), 50/50 MeCN/0.2% H<sub>3</sub>PO<sub>4</sub>, 1.0 mL/min, product = 7.8 min) or by TLC analysis (2-fluoroanisole R<sub>f</sub> = 0.67, product R<sub>f</sub> = 0.51, ethyl acetate/hexanes 20/80).
6. A.C.S. Reagent grade methyl tert-butyl ether was purchased from J. T. Baker and used as received.
7. <sup>1</sup>H NMR and <sup>13</sup>C NMR indicate reasonably pure product. The HPLC analysis of the crude product showed a purity >97% (same conditions as Note 5) and satisfactory elementary analysis (calculated for C<sub>11</sub>H<sub>13</sub>NO: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.01; H, 7.35; N, 8.07).
8. The product shows the following physical properties: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ: 1.80 (s, 6), 3.96 (s, 3), 6.97-7.02 (m, 2), 7.29-7.39 (m, 2); <sup>13</sup>C NMR δ: 27.00, 34.43, 55.51, 112.02, 120.76, 124.80, 125.92, 128.62, 129.39, 157.30. IR cm<sup>-1</sup>: 2980, 2235, 1493, 1462, 1437, 1253, 1027, 756.
9. If material of greater purity is necessary, the product can be purified by chromatography on silica gel (100 g) using ethyl acetate/hexanes 20/80 (900 mL) as the eluant. When 100-mL fractions were collected, fractions #2 to #5 contained the desired product in >99% purity (12.31g, 89% yield).

### Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory,"

### 3. Discussion

Tertiary benzylic nitriles are useful synthetic intermediates, and have been used for the preparation of amidines,<sup>2</sup> lactones,<sup>3</sup> primary amines,<sup>4-5</sup> pyridines,<sup>6</sup> aldehydes,<sup>7-8</sup> carboxylic acids,<sup>9</sup> and esters.<sup>10-11</sup> The general synthetic pathway to this class of compounds relies on the displacement of an activated benzylic alcohol or benzylic halide with a cyanide source followed by double alkylation under basic conditions. For instance, 2-(2-methoxyphenyl)-2-methylpropionitrile has been prepared by methylation of (2-methoxyphenyl)acetone using sodium amide and iodomethane.<sup>12</sup> In the course of the preparation of a drug candidate,<sup>13</sup> the submitters discovered that the nucleophilic aromatic substitution of aryl fluorides with the anion of a secondary nitrile is an effective method for the preparation of these compounds.<sup>14</sup> The reaction was studied using isobutyronitrile and 2-fluoroanisole. The submitters first showed that KHMDS was the superior base for the process when carried out in either THF or toluene (Table I). For example, they found that the preparation of 2-(2-methoxyphenyl)-2-methylpropionitrile could be accomplished in near quantitative yield in a single operation. Several other substrates were studied as summarized in Table II. The reaction proceeds using either electron-rich or electron-poor arenes (entries 1-11) as well as cyclic nitriles (entries 12-14). The reaction requires an excess of nitrile, which can self-condense under the reaction conditions, as well as a slight excess of base. The submitters obtained the best results when using about 1.5 equiv of base in conjunction with 4 equiv of the nitrile. The acidic work-up removes most of the impurities generated in the reaction and, in the case of a low boiling starting nitrile, the excess reagent is evaporated with the solvent to provide a crude material of high purity.

TABLE I  
NUCLEOPHILIC AROMATIC SUBSTITUTION OF (2-METHOXYPHENYL)-  
ACETONITRILE WITH ISOBUTYRONITRILE

Entry	Base (1.5 equiv)	Solvent	T (°C)	Time (h)	Yield <sup>a</sup> (%)
1	LiHMDS	THF	60	23	3
2	NaHMDS	THF	60	23	49
3	KHMDS	THF	60	23	95
4	KHMDS	Toluene	60	18	95
5	KHMDS	DMSO	75	24	No rxn
6	KHMDS	i-Pr <sub>2</sub> O	75	24	3
7	KHMDS	NMP	75	24	1

a) Yields <5% indicates the conversion observed by HPLC analysis after the time shown. The yields of entry 2,3 and 4 are isolated yields.

TABLE II  
S<sub>N</sub>ArOF ARYL FLUORIDES WITH SECONDARY  
NITRILES AND KHMDS

Entry	Fluoride	Nitrile (equiv)	Solvent	T (°C)	Time	Yield (%)
1	2-OMe	1 (4.0)	Toluene	60	18 h	99
2	3-OMe	1 (4.1)	Toluene	100	3 h	69
3	4-OMe	1 (4.0)	THF	60	50 h	66
4	3,5-OMe	1 (4.0)	Toluene	70	48 h	85
5	3,4-OMe	1 (4.0)	THF	80	4 h	28
6	2-Cl	1 (4.0)	Toluene	60	45 min	77
7	4-Cl	1 (4.0)	THF	75	2 h	72

8	H	<b>1</b> (4.0)	THF	75	14 h	69
9	3-Me	<b>1</b> (4.0)	THF	75	14 h	71
10	4-CN	<b>1</b> (4.0)	Toluene	60	40 min	83
11	4-CF <sub>3</sub>	<b>1</b> (3.3)	Toluene	60	40 min	94
12	2-OMe	<b>2</b> (4.0)	Toluene	75	48 h	47
13	2-OMe	<b>3</b> (4.0)	THF	75	24 h	67 <sup>a</sup>
14	2-OMe	<b>4</b> (4.0)	THF	75	15 h	70 <sup>a</sup>

a) Provided exclusively the 2(*S*) isomer (*exo*-aryl).

## References and Notes

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## Appendix

### Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-(2-Methoxyphenyl)-2-methylpropionitrile:  
Hydratropionitrile, o-methoxy- $\alpha$ -methyl- (8);  
Benzeneacetonitrile, 2-methoxy- $\alpha,\alpha$ -dimethyl- (9); (13524-75-9)

2-Fluoroanisole:  
Anisole, o-fluoro- (8);  
Benzene, 1-fluoro-2-methoxy- (9); (321-28-8)

Potassium hexamethyldisilylamide: Aldrich:  
Potassium-(bis(trimethylsilyl)amide):  
Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, potassium salt (9); (40949-94-8)

Isobutyronitrile (8):  
Propanenitrile, 2-methyl- (9); (78-82-0)

