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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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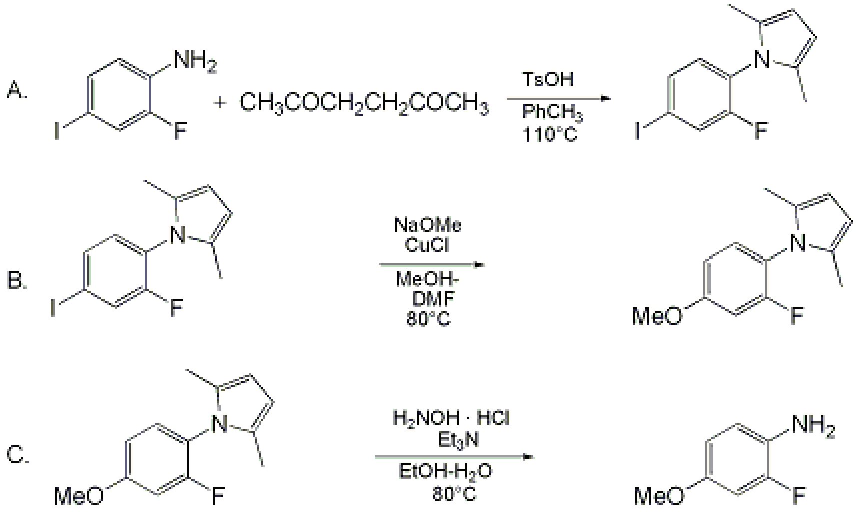
ULLMAN METHOXYLATION IN THE PRESENCE OF A 2,5-DIMETHYLPYRROLE-BLOCKED ANILINE: PREPARATION OF 2-FLUORO-4-METHOXYANILINE

[Benzenamine, 2-fluoro-4-methoxy-]



Submitted by John A. Ragan, Brian P. Jones, Michael J. Castaldi, Paul D. Hill, and Teresa W. Makowski[1] .
Checked by Samuel W. Ridenour and David J. Hart.

1. Procedure

A. 1-(2-Fluoro-4-iodophenyl)-2,5-dimethyl-1H-pyrrole . A 500-mL, single-necked, round-bottomed flask with a Teflon-coated magnetic stir bar is charged with 2-fluoro-4-iodoaniline (50.0 g, 211 mmol) (Note 1), p-toluenesulfonic acid (0.40 g, 2.1 mmol) (Note 2), 250 mL of toluene (Note 3), and acetonylacetone(29.7 mL, 253 mmol) (Note 4). A Dean-Stark trap is attached to the flask, and the solution is warmed to reflux for 1 hr (Note 5). After the solution is cooled to room temperature, it is transferred to a 500-mL separatory funnel, and washed with one 50-mL portion of aqueous saturated sodium bicarbonate ($NaHCO_3$), five 50-mL portions of water (Note 6), and one 50-mL portion of brine. The organic phase is dried over anhydrous magnesium sulfate ($MgSO_4$), filtered, and concentrated to provide a brown, free-flowing solid (67.5 g, 101.5% of theory) (Notes 7 and 8).

B. 1-(2-Fluoro-4-methoxyphenyl)-2,5-dimethyl-1H-pyrrole . A 500-mL, single-necked, round-bottomed flask equipped with a condenser and Teflon-coated magnetic stir bar is flame-dried under a positive pressure of nitrogen, and charged with 1-(2-fluoro-4-iodophenyl)-2,5-dimethyl-1H-pyrrole (66.6 g, 211 mmol) , sodium methoxide (NaOMe) (34.2 g, 633 mmol) (Note 9), copper(I) chloride (3.13 g, 31.7 mmol) (Note 10), 230 mL of methanol (Note 11) and 70 mL of dimethylformamide (DMF) (Note 12). The resulting slurry is placed in an 80°C oil bath for 90 min (Note 13) so that a gentle reflux is maintained, then cooled to room temperature. The slurry is poured into a rapidly stirring mixture of 500 mL of isopropyl ether (Note 14), 220 mL of aq 5% ammonium chloride (NH_4Cl) (Note 15), and 350 mL of water in a 2-L Erlenmeyer flask, rinsing with several small portions of methanol. The resulting slurry is stirred overnight (Note 16). It is filtered through a 3"-pad of Celite in a coarse-frit glass funnel, and the filtrate is transferred to a 2-L separatory funnel. The phases are separated, and the aqueous phase is extracted with three 50-mL portions of isopropyl ether . The combined organic phases are washed with 200 mL of aqueous 10% NH_4OH (Note 17), filtered through a silica gel pad (Note 18), and concentrated to provide a brown, free-flowing solid (42.0 g, 92% crude yield) (Note 19). The crude product is recrystallized by dissolving it in 100 mL of hot hexanes and stirring overnight at room temperature, then collecting the resulting brown solid (34.7 g, 75% yield) (Note 20).

C. 2-Fluoro-4-methoxyaniline . A 1-L, single-necked flask equipped with a reflux condenser and Teflon-coated magnetic stirring bar is charged with 1-(2-fluoro-4-methoxyphenyl)-2,5-dimethyl-1H-pyrrole (34.7 g, 158 mmol) , hydroxylamine hydrochloride (110 g, 1.58 mol) (Note 21), triethylamine (44.0 mL, 316 mmol) (Note 22), 300 mL of 95% ethanol, and 150 mL of water. The resulting solution is warmed to reflux for 20 hr (Notes 23 and 24), then cooled to room temperature. The reaction is quenched by pouring into a rapidly stirred solution of 200-300 mL of ice-cold 1 N hydrochloric acid (HCl). This solution is washed with two 250-mL portions of isopropyl ether , the pH is adjusted to 9-10 by careful addition of 6 N sodium hydroxide (NaOH), and the resulting mixture is extracted with two 250-mL portions of isopropyl ether . The final organic phase is dried over $MgSO_4$, filtered, and concentrated to an oily, brown solid. This material is triturated with several portions of isopropyl ether with warming on a steam bath to dissolve as much product as possible, decanting away from an insoluble cream colored solid (Note 25). Concentration of these extracts provides a brown solid (18.1 g, 81% crude yield), which is recrystallized by dissolving in 18 mL of hot isopropyl ether , and slowly adding 80 mL of hexanes. After the product is placed in an ice bath for 1 hr, it is isolated as a brown solid (16.0 g, 72% yield), which is further purified by trituration at room temperature with 160 mL of water for 16 hr (Note 26): filtration and drying in a vacuum oven (with little if any heating) provide analytically pure product: 13.0 g, 58% yield (Note 27).

2. Notes

1. 2-Fluoro-4-iodoaniline was obtained from Aldrich Chemical Company, Inc. , and used without further purification. It can also be prepared by iodination of 2-fluoroaniline.[2]
2. p-Toluenesulfonic acid monohydrate was obtained from Aldrich Chemical Company, Inc. , and used without further purification.
3. A.C.S. reagent grade toluene was obtained from J. T. Baker and used as received.
4. Acetonylacetone(hexane-2,5-dione) was obtained from Aldrich Chemical Company, Inc. , and used without further purification.
5. The reaction can be monitored by TLC (20:1 hexane-ethyl acetate , UV visualization, SM $R_f = 0.11$, product $R_f = 0.56$). The submitters indicate that the reaction can also be monitored by GC/MS (Hewlett-Packard 5890 GC/MS, HP-1 column (12 m×0.2 mm×0.33 μm), 1 mL/min flow rate, injector temp. 280° C, oven temp. 133°C for 0.1 min, then ramp 19°C/min to 310°C, hold for 1.65 min): SM $R_f = 1.53$ min, product $R_f = 3.10$ min.
6. Multiple aqueous washes assist in removing any excess acetonylacetone.
7. ^{1}H NMR indicates reasonably pure product, with trace amounts of toluene and acetonylacetone.
8. The product shows the following physical properties: mp 68-70°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.03 (s, 6 H), 5.94 (s, 2 H), 7.02 (t, 1 H, J = 8), 7.64 (m, 2 H) ; ^{13}C NMR ($CDCl_3$) (8 of 9 lines observed) δ: 12.5, 92.8, 106.5, 126.1 (d, J = 23), 128.9, 131.9, 134.0 (d, J = 4), 158.1 (d, J = 254) ; MS (EI): m/z 268 (100) ; HRMS (FAB) calcd for $C_{12}H_{11}NFI$ (M^+) 315.9999, found 315.9995.
9. Sodium methoxide was obtained from Aldrich Chemical Company Inc. , and used without further purification. Out of a total of five separate batches of NaOMe (all new, unopened bottles) used over a 24-month period, the submitters had one occasion where the reaction failed to proceed beyond 15-20% conversion. When a new bottle of NaOMe (different lot number) was used, the reaction worked as usual. The NaOMe that failed in the Ullman coupling was found to have limited solubility in methanol (MeOH) (bottles that worked displayed MeOH solubilities of >100 mg/mL), suggestive of contamination by significant quantities of NaOH, possibly from adventitious water introduced during re-packaging or manufacture.
10. Cuprous chloride (CuCl) was obtained from Aldrich Chemical Company, Inc. , and used without further purification.
11. A.C.S. reagent grade methanol was obtained from J. T. Baker and used as received.
12. Sure-seal DMF was obtained from Aldrich Chemical Company, Inc. , and used as received.
13. The submitters indicate that the reaction can be monitored by GC/MS (same conditions as (Note 5)): SM $R_f = 3.10$ min, product $R_f = 2.50$ min.
14. A.C.S. reagent grade isopropyl ether was obtained from J. T. Baker and used as received.
15. The ammonium chloride solution was prepared by dissolution of 50 g of NH_4Cl (Aldrich Chemical Company, Inc.) in 950 mL of distilled water.

16. The Erlenmeyer is loosely capped with a piece of aluminum foil or a cork stopper. The submitters have run this step, which assists in removal of copper salts, for as short as 16 hr to as long as 60 hr with no change in outcome.

17. The ammonium hydroxide was prepared by dilution of commercial 28-30% NH_4OH (Baker) with 9 volumes of distilled water.

18. Silica gel, 100 g of 230-400 mesh, was used in an 8-cm diameter, medium-frit glass funnel.

19. The crude product is quite pure by ^1H NMR, and can be carried directly into the deprotection if desired.

20. The product shows the following physical properties: mp 67-69°C; H NMR (400 MHz, $CDCl_3$) δ:1.97 (s, 6 H), 3.82 (s, 3 H), 5.89 (s, 2 H), 6.73 (s, 1 H), 6.75 (d, 1 H, J = 8), 7.12 (t, 1 H, J = 8) ; ^{13}C NMR ($CDCl_3$) (9 of 10 lines observed) δ: 12.4, 55.7, 102.3 (d, J = 25), 105.6, 106.0, 109.9 (d, J = 3), 129.5, 130.7, 159.1 (d, J = 260) ; MS (EI): m/z 219 (100); HRMS (FAB) calcd for $C_{13}H_{14}NFO$ (M+H) 220.1138, found 220.1127. Product color ranges from light brown to dark brown with no effect on physical and spectral properties.

21. Hydroxylamine hydrochloride was obtained from Fisher Scientific Company and used as received.

22. A.C.S. reagent grade triethylamine was obtained from J. T. Baker and used as received.

23. Because of the potentially explosive nature of hydroxylamine [3] the reaction should be kept behind a blast shield while heating.

24. The submitters indicate that the reaction can be monitored by GC/MS (same conditions as Note 5): SM $R_f = 2.50$ min, product $R_f = 0.90$ min.

25. ^1H NMR of this material shows just two singlets (δ 2.48 and 1.91), suggesting that it is derived from acetonylacetone (possibly the bis-oxime).

26. This water reslurry serves to remove trace residues of the δ 2.48 and 1.91 impurity referred to in Note 25.

27. The product shows the following physical properties (ref 4): mp 46.8-47.1°C; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.34 (br s, 2 H), 3.72 (s, 3 H), 6.53 (m, 1 H), 6.61 (dd, 1 H, J = 3, 10), 6.72 (dd, 1 H, J = 9, 10) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ:56.2, 102.7, 110.2, 118.1, 128.1, 153.3, 152.4 . Anal. Calcd for C_7H_8NFO: C, 59.57; H, 5.71; N, 9.92. Found: C, 59.62; H, 5.74; N, 9.99. The product color ranges from light brown to dark brown with no effect on physical or spectral properties.

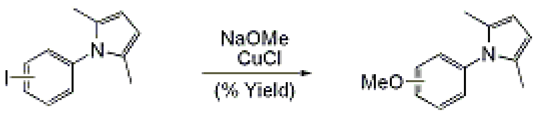
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

2-Fluoro-4-methoxyaniline has been previously prepared by nitration of 2-fluorophenol [5] followed by alkylation with dimethyl sulfate and reduction of the nitro group.[4] Nitration delivers a mixture of regioisomers that require chromatographic separation. The submitters recently required a practical, multi-gram synthesis of this compound, and concerns with the potential thermal hazards of a nitration reaction, poor nitration regioselectivity, and handling of dimethyl sulfate led them to investigate an alternative synthesis. The commercial availability of 2-fluoro-4-iodoaniline motivated them to investigate an Ullman coupling.[6]They investigated a variety of blocking groups for the aniline moiety (the unprotected aniline failed to couple under standard conditions), and found the 2,5-dimethylpyrrole blocking group to be uniquely suited for this purpose.[7]Several other substrates were also investigated, as summarized in the Table. Interestingly, electron-withdrawing groups on the aromatic ring led to significantly lower yields (e.g., entries 7 and 8). However, the regiochemistry between the 2,5-dimethylpyrrole substituent and the iodide was of little consequence to the yield of methoxylation.

TABLE



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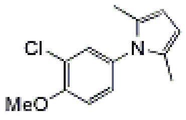
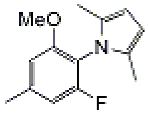
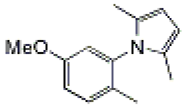
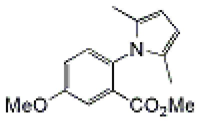
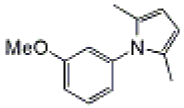
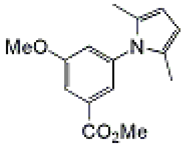
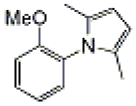
	96		97
	95		0
	92		34
	94		

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

2-Fluoro-4-methoxyaniline (8,9); (458-52-6)

1-(2-Fluoro-4-iodophenyl)-2,5-dimethyl-1H-pyrrole:
1H-Pyrrole, 1-(2-fluoro-4-iodophenyl)-2,5-dimethyl- (14); (217314-30-2)

2-Fluoro-4-iodoaniline:

Aniline, 2-fluoro-4-iodo- (8,9); (29632-74-4)

p-Toluenesulfonic acid monohydrate (8);
Benzenesulfonic acid, 4-methyl-, monohydrate (9); (6192-52-5)

Acetonylacetone:
2,5-Hexanedione (8,9); (110-13-4)

1-(2-Fluoro-4-methoxyphenyl)-2,5-dimethyl-1H-pyrrole:
1H-Pyrrole, 1-(2-fluoro-4-methoxyphenyl)-2,5-dimethyl- (14); (217314-31-3)

Sodium methoxide:
Methanol, sodium salt (8,9); (124-41-4)

Copper(I) chloride:
Copper chloride (8,9); (7758-89-6)

N,N-Dimethylformamide:CANCER SUSPECT AGENT:
Formamide, N,N-dimethyl- (8,9); (68-12-2)

Hydroxylamine hydrochloride (8);
Hydroxylamine, hydrochloride (9); (5470-11-1)