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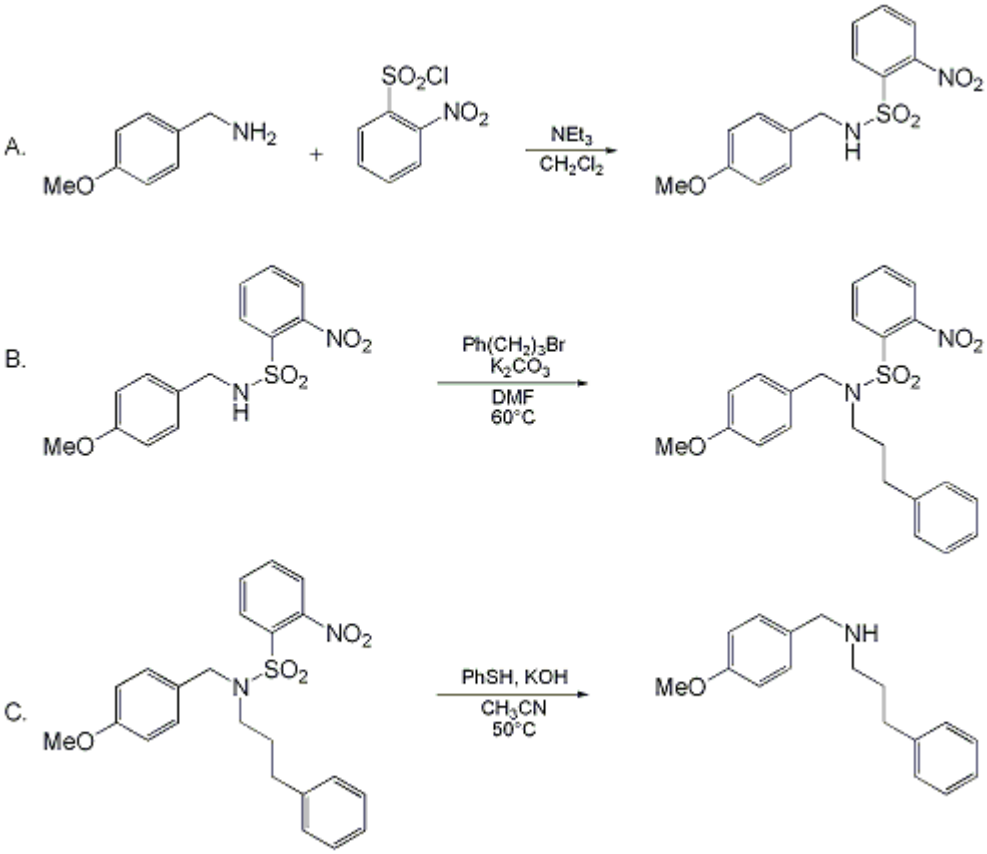
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.079.0186

Organic Syntheses, Coll. Vol. 10, p.482 (2004); Vol. 79, p.186 (2002).

PREPARATION OF SECONDARY AMINES FROM PRIMARY AMINES VIA 2-NITROBENZENESULFONAMIDES: N-(4-METHOXYBENZYL)-3-PHENYLPROPYLAMINE

[Benzenepropanamine, N-[(4-methoxyphenyl)methyl]-]



Submitted by Wataru Kurosawa, Toshiyuki Kan, and Tohru Fukuyama[1] .
Checked by Audra M. Dalton and Rick L. Danheiser.

1. Procedure

A. N-(4-Methoxybenzyl)-2-nitrobenzenesulfonamide . A 300-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen gas inlet, and a rubber septum is charged with 6.81 g (49.6 mmol) of 4-methoxybenzylamine (Note 1), 100 mL of dichloromethane and 6.93 mL (49.6 mmol) of triethylamine (Note 1). The mixture is stirred and cooled in an ice-water bath while 10.0 g (45.1 mmol) of 2-nitrobenzenesulfonyl chloride (Note 1) is added over a period of 5 min. After 5 min, the ice bath is removed and the reaction mixture is allowed to warm to room temperature, stirred for 15 min (Note 2), and then quenched with 100 mL of 1N hydrochloric acid (HCl). The aqueous layer is extracted with two 100-mL portions of dichloromethane , and the combined organic extracts are washed with 50 mL of brine, dried over magnesium sulfate , filtered, and concentrated under reduced pressure to give 14.2 g (98%) of the crude 2-nitrobenzenesulfonamide . Recrystallization from 500 mL of 1:1 ethyl acetate/hexane gives 13.00-13.15 g (90-91%) of N-(4-Methoxybenzyl)-2-nitrobenzenesulfonamide as white crystals (Note 3).

B. N-(4-Methoxybenzyl)-N-(3-phenylpropyl)-2-nitrobenzenesulfonamide . A 200-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, a nitrogen gas inlet, and a rubber septum is

charged with 10.0 g (31.0 mmol) of N-(4-Methoxybenzyl)-2-nitrobenzenesulfonamide, 12.9 g (93.1 mmol) of potassium carbonate (Note 4), and 40 mL of anhydrous dimethylformamide (DMF). To the stirred mixture is added 5.19 mL (34.1 mmol) of 3-phenylpropyl bromide (Note 5) over a period of 5 min and the resulting mixture is heated in a 60°C oil bath for 70 min (Note 6). The reaction mixture is allowed to cool to room temperature, diluted with 250 mL of water, and extracted with three 250-mL portions of ether. The combined organic extracts are washed with brine (100 mL), dried over magnesium sulfate , filtered, and concentrated under reduced pressure to give a pale yellow liquid. The residue is purified by column chromatography on silica gel (Note 7) to give 13.5 g (99%) of N-(4-Methoxybenzyl)-N-(3-phenylpropyl)-2-nitrobenzenesulfonamide (Note 8) as a viscous pale yellow liquid.

C. N-(4-Methoxybenzyl)-3-phenylpropylamine . A 100-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen gas inlet, and a rubber septum is charged with 7.82 mL (76.5 mmol) of thiophenol (Note 9) and 20 mL of acetonitrile (CH_3CN). The mixture is cooled in an ice-water bath and 10.9 M aqueous potassium hydroxide solution (7.02 mL, 76.5 mmol) is added over a period of 10 min. After 5 min, the ice-water bath is removed, and 13.5 g (30.6 mmol) of N-(4-Methoxybenzyl)-N-(3-phenylpropyl)-2-nitrobenzenesulfonamide in 20 mL of acetonitrile is added over 20 min. The reaction mixture is heated in a 50°C oil bath for 40 min (Note 10). The reaction mixture is allowed to cool to room temperature, diluted with 80 mL of water, and extracted with three 80-mL portions of dichloromethane . The combined organic extracts are washed with brine (80 mL), dried over magnesium sulfate , filtered, and concentrated under reduced pressure. The residue is purified by column chromatography on silica (Note 11) to give 7.81 g of the desired amine and its hydrochloride salt. This oil is dissolved in 120 mL of dichloromethane and washed with two 80-mL portions of 1 M aqueous sodium hydroxide solution, 40 mL of brine, dried over magnesium sulfate , filtered, and concentrated under reduced pressure. Bulb-to-bulb distillation (0.25 mm, oven temperature 150°C) provides 6.98-7.08 g (89-91%) of N-(4-Methoxybenzyl)-3-phenylpropylamine as a colorless oil (Notes 12, 13).

2. Notes

1. 4-Methoxybenzylamine , triethylamine , and 2-nitrobenzenesulfonyl chloride were purchased by the submitters from Tokyo Kasei Kogyo Co. The checkers obtained 4-methoxybenzylamine and 2-nitrobenzenesulfonyl chloride from Alfa Aesar and triethylamine from Mallinckrodt Inc. .
2. All reactions were monitored by TLC analysis on Merck silica gel 60 F254 plates, which were visualized by a 254-nm UV lamp and stained with an ethanolic solution of phosphomolybdic acid . TLC analysis showed clean formation of the 2-nitrobenzenesulfonamide (hexane : ethyl acetate 3 : 2, R_f = 0.33).
3. Yield is based on 2-nitrobenzenesulfonyl chloride . The crude product was practically pure as judged by ^{1}H NMR analysis and may be used for the next step without purification. The recrystallized compound exhibits the following properties: mp 123°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.76 (s, 3 H), 4.25 (d, 2 H, J = 6.2), 5.63 (br, t, 1 H, J = 6.2), 6.75 (d, 2 H, J = 8.5), 7.13 (d, 2 H, J = 8.5), 7.63-8.03 (m, 4 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 47.4, 55.3, 114.0, 125.2, 127.7, 129.2, 131.1, 132.7, 133.3, 134.0, 159.3 ; IR (thin film) cm^{-1}: 3312, 2941, 1543, 1511, 1363, 1337, 1243, 1160 ; MS m/z: 322, 134, 121 . Anal. Calcd for $C_{14}H_{14}N_2O_5S$: C, 52.17; H, 4.38; N, 8.69. Found: C, 52.05; H, 4.46; N, 8.74.
4. The checkers obtained anhydrous DMF from EM Sciences. Potassium carbonate (powder, K2CO3) was purchased from Aldrich Chemical Company, Inc. If granular K_2CO_3 is used in place of powder, the reaction requires a longer time (5.5 hr) and proceeds in lower yield (81%).
5. 3-phenylpropyl bromide was purchased from Tokyo Kasei Kogyo Co. or Alfa Aesar.
6. TLC analysis showed clean formation of the alkylated sulfonamide (hexane : ethyl acetate 1 : 1, R_f = 0.71).
7. Column chromatography was performed on 150 g of silica gel (100-210 µm, Kanto Chemical Co., Inc. or Silacycle, Inc.). The product was eluted with 300 mL of 10% ethyl acetate-hexane , 300 mL of 25% ethyl acetate-hexane , and 1.8 L of 40% ethyl acetate-hexane , and 300-mL fractions were collected.
8. The product exhibits the following properties: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.70 (dt, 2 H, J = 7.7, 7.7), 2.44 (t, 2 H, J = 7.7), 3.23 (t, 2 H, J = 7.7), 3.79 (s, 3 H), 4.44 (s, 2 H), 6.81 (d, 2 H, J = 8.7), 6.99 (d, 2 H, J = 8.7), 7.14-7.25 (m, 5 H), 7.58-7.92 (m, 4 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.0, 32.6,

46.4, 50.7, 55.2, 114.0, 124.1, 125.9, 127.5, 128.2, 128.3, 129.7, 130.7, 131.6, 133.3, 133.6, 140.9, 147.8, 159.5 ; IR (neat) cm^{-1}: 2934, 1543, 1513, 1372, 1346, 1250, 1211 ; MS m/z 440, 150, 122 . Anal. Calcd for $C_{23}H_{24}N_2O_5S$: C, 62.71; H, 5.49; N, 6.36. Found: C, 62.76; H, 5.47; N, 6.31.

9. Thiophenol and potassium hydroxide were purchased by the submitters from Tokyo Kasei Kogyo Co. and by the checkers from Aldrich Chemical Company, Inc. and Mallinckrodt Inc. , respectively.

10. TLC analysis showed clean formation of the deprotected amine (methanol:dichloromethane 10 : 90, $R_f = 0.52$).

11. Column chromatography was performed on 150 g of silica gel (100-210 µm, Kanto Chemical Co., Inc. or Silacycle, Inc.). The product was eluted with 70 mL of dichloromethane , 900 mL of 2% methanol-dichloromethane , and 1.8 L of 2.5:2.5:95 isopropylamine-methanol-dichloromethane (300-mL fractions).

12. The product exhibits the following properties: ^1H NMR (400 MHz, $CDCl_3$) δ: 1.83 (dt, 2 H, J = 7.8, 7.8), 2.65 (m, 4 H), 3.71 (s, 2 H), 3.79 (s, 3 H), 6.84-7.28 (m, 9 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.6, 33.6, 48.7, 53.4, 55.1, 113.8, 125.8, 128.3, 129.2, 132.6, 142.1, 158.5 ; IR (neat) $cm^{-1:}$ 3302, 2931, 1511, 1246 ; MS m/z 255, 150, 121 . Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.76; H, 8.40; N, 5.41.

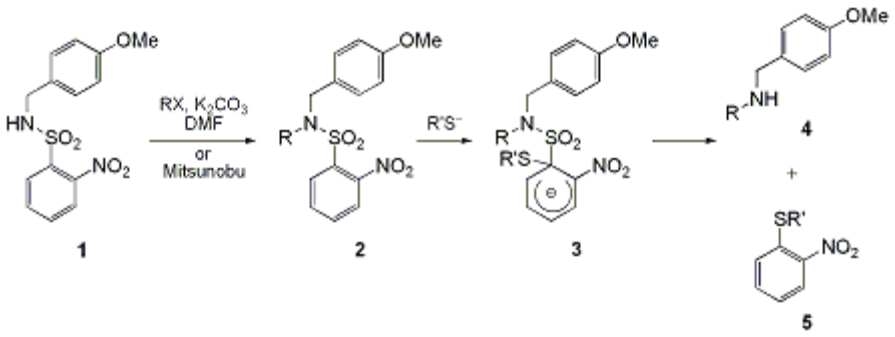
13. The amine can be transformed to the hydrochloride salt by bubbling a stream of hydrogen chloride gas into a solution of 7.81 g of the amine in methanol at 0°C. Recrystallization from 2-propanol gives N-(4-methoxybenzyl)-3-phenylpropylamine hydrochloride (7.92 g, 88%) as white crystals. The product exhibits the following properties: mp 206°C; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.14 (dt, 2 H, J = 7.4, 7.7), 2.62 (t, 2 H, J = 7.4), 2.73 (t, 2 H, J = 7.7), 3.74 (s, 3 H), 3.91 (s, 2 H), 6.87 (d, 2 H, J = 8.6), 7.10-7.24 (m, 5 H), 7.45 (d, 2 H, J = 8.6), 9.80 (br, s, 1 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.0, 32.5, 44.9, 49.8, 55.1, 114.2, 121.8, 126.1, 128.2, 128.4, 131.8, 139.7, 160.2 ; IR (thin film) cm^{-1}: 2938, 2789, 1518, 1252 ; MS m/z 255, 150, 121 . Anal. Calcd for $C_{17}H_{22}ClNO$: C, 69.97; H, 7.60; N, 4.80. Found: C, 69.85; H, 7.58; N, 4.86.

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

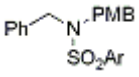
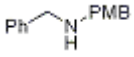
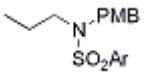
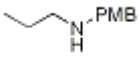
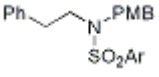
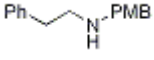
Conversion of primary amines to the corresponding secondary amines appears to be deceptively simple.[2] Alkylation of primary amines with alkyl halides or sulfonates frequently leads to the formation of the undesired tertiary amines and/or quaternary ammonium salts. Reductive alkylation with aldehydes or ketones using sodium cyanoborohydride ($NaBH_3CN$) often produces tertiary amines to a varying extent unless the desired secondary amine is sterically hindered. Reduction of N-monoalkyl amides with such strong reducing agents as lithium aluminum hydride ($LiAlH_4$), diisobutylaluminum hydride (DIBAL), or borane seems to be the most reliable procedure. To circumvent these problems, the Mitsunobu alkylations of toluenesulfonamides[3] and trifluoroacetamides[4] have recently been reported. However, because of the relatively harsh deprotection conditions, these methods do not appear to be suitable for the preparation of the base-sensitive secondary amines. The present procedure describes the simple and general transformation of primary amines to the corresponding secondary amines using the 2-nitrobenzenesulfonamide protecting group that can be applied to the synthesis of a wide range of secondary amines (Scheme 1).[5] A related procedure using 2,4-dinitrobenzenesulfonamides that requires even milder deprotection conditions ($HSCH_2CO_2H$, Et_3N, CH_2Cl_2, room temperature) has recently been reported.[6]

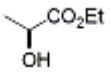


Protection of the primary amines was performed by treatment with 2-nitrobenzenesulfonyl chloride and base (triethylamine, pyridine, or 2,6-lutidine) to give N-monosubstituted 2-nitrobenzenesulfonamides in high yields (Step A). Alkylation of N-monosubstituted 2-nitrobenzenesulfonamides (1) proceeded smoothly under either the conditions described above (conventional) or Mitsunobu conditions[7] to give N,N-disubstituted 2-nitrobenzenesulfonamide (2) in excellent yields. For large-scale alkylations, conventional conditions are recommended, because of the ease of purification. Facile deprotection of N,N-disubstituted 2-nitrobenzenesulfonamides is achieved by treatment with thiolate nucleophile, presumably via the formation of a Meisenheimer complex[8] (3), giving the desired secondary amines (4) in excellent yields (Step C). Since potassium hydroxide is inexpensive, the described procedure is convenient for a large-scale reaction. For a small scale reaction, however, one of the following reported procedures is recommended: (1) potassium carbonate , thiophenol in DMF, (2) cesium carbonate , thiophenol in CH_3CN, (3) lithium hydroxide , mercaptoacetic acid in DMF. Procedure (3) has the advantage that the by-product 2-nitrophenylthioacetic acid (5) can be easily removed by partitioning between ether and an aqueous sodium bicarbonate solution. Representative examples of this protocol are summarized in Table I.

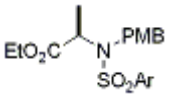
Since the 2-nitrobenzenesulfonamide group is stable under acidic [HCl (10 eq), MeOH, 60°C, 4 hr] as well as basic [NaOH (10 eq), MeOH, 60°C, 4 hr] conditions, it can be used extensively for protection of primary and secondary amines. Because of the mild conditions and easy procedure, the submitters believe that the use of 2-nitrobenzenesulfonamides serves as a method of choice for the preparation of a wide variety of secondary amines comparable to the Gabriel synthesis for primary amines.

TABLE 1
ALKYLATION AND DEPROTECTION OF 2-NITROBENZENESULFONAMIDES

RX or ROH	Alkylation conditions[a]	2[b](% isolated yield)	Deprotection conditions[c]	4[b,d](%isolated yield)
	A	 (98)	TP	 (94)
			MA	(93)
	B	 (98)	TP	 (94)
	C	 (91)	TP	 (88)

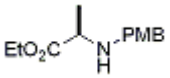


C



(87)

TP



(93)

[a]A: RX (1.1 eq), K_2CO_3 (2 eq), DMF, 23°C, 1 hr.
B: RX (1.1 eq), K_2CO_3 (2 eq), DMF, 60°C, 30 min.
C: ROH (1.3 eq), DEAD (1.3 eq), PPh_3 (1.3 eq), CH_2Cl_2, 23°C, 1 hr.
[b]Satisfactory spectroscopic data were obtained on all new compounds.
[c]TP: PhSH (1.2 eq), K_2CO_3 (3 eq), DMF, 23°C, 40 min.
MA: $HSCH_2CO_2H$ (2 eq), LiOH (4 eq), DMF, 23 °C, 1 hr.
[d]Separated by silica gel chromatography after partitioning between Et_2O and a dilute $NaHCO_3$ solution.

References and Notes

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

N-(4-Methoxybenzyl)-3-phenylpropylamine:
Benzenepropanamine, N-[(4-methoxyphenyl)methyl]- (13); (145060-50-0)

N-(4-methoxybenzyl)-2-nitrobenzenesulfonamide:
Benzenesulfonamide, N-[(4-methoxyphenyl)methyl]-2-nitro- (13); (171414-16-7)

4-Methoxybenzylamine:
Benzylamine, p-methoxy- (8);
Benzenemethaneamine, 4-methoxy- (9); (2393-23-9)

Triethylamine (8):
Ethanamine, N,N-diethyl- (9); (121-44-8)

o-Nitrobenzenesulfonyl chloride:
Benzenesulfonyl chloride, o-nitro- (8);

Benzenesulfonyl chloride, 2-nitro- (9); (1694-92-4)

3-Phenylpropyl bromide: ALDRICH:
1-Bromo-3-phenylpropane: Benzene, (3-bromopropyl)- (8,9); (637-59-2))

Thiophenol:
Benzenethiol (13); (108-98-5)