A Convenient Method for Direct *N-tert*-Butylation of Aromatic Amines

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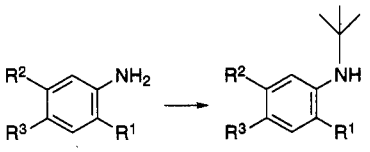
Although the synthesis of *tert*-butyl ethers by acid-catalyzed reaction of an alcohol and a *tert*-butyl cation source is one of the classical methods of organic chemistry, the corresponding *tert*-alkylation reaction of primary or secondary amines has not proven generally useful. Acids strong enough to generate *tert*-butyl cations from isobutylene first protonate the more basic amine, rendering it non-nucleophilic. Previously reported conditions suffer from low conversion and/or, for aromatic substrates, produce substantial amounts of ring-alkylated materials.[1-3] We disclose in this paper a convenient one-step method for *N-tert*-butylation of aromatic amines.



(1)

Aromatic amines were heated with a mixture of 1,4-dioxane and isobutylene in a pressure tube at temperatures ranging from 90 to 140 °C in the presence of 48% aqueous HBr. Substrates with pK_a's below ~4 reacted smoothly at or below 110 °C in the presence of a full equivalent of acid (Table 1, entries 1–5). Conversion of 2-nitroaniline was low because of an unfavorable location of the equilibrium between starting material and product (entry 5), a phenomenon demonstrated by isolation of the product and resubmission to the reaction conditions. However, the reactions were very clean; generally only starting material and the desired alkylation product were observed. No trace of di-*tert*-butylation was detected for any of the substrates presented in the table. Data for a typical substrate, 2-fluoroaniline (pK_a 3.2), showing the extent of conversion as a function of time and temperature, are collected in Table 2.

Substoichiometric amounts of acid in conjunction with higher temperatures were most effective for those substrates with pK_a's in the 4–6 range. Once again, only starting material and product were observed in the reaction mixture, and isolated yields merely reflect the extent of conversion at the time that the reaction was stopped. Alternatively, 1 equiv of pyridine could be added to these reactions in order to increase the concentration of the free aniline, although this modification tended to result in formation of some ring-alkylated material for the more nucleophilic substrates, especially *m*-anisole. Results are collected in Table 1. Notably, acceptable results were obtained even when the starting amine contained an ortho substituent (entries 6 and 9). Although column chromatography was used to isolate the products in this study, in most instances the product and starting material are readily separated by distillation, a more appropriate method for larger preparations. Also,

Table 1. *tert*-Butylation of Aromatic Amines with Isobutylene and HBr

entry	starting material	pK_a	method[a]	product	% yield[b]
1	R^1 = Cl R^2, R^3 = H	2.6	A	**1**	78
2	R^3 = Cl R^1, R^2 = H	4.0	A	**2**	74
3	R^1 = F R^2, R^3 = H	3.2	A	**3**	81
4	R^3 = NO_2 R^1, R^2 = H	1.0	A	**4**	80
5	R^1 = NO_2 R^2, R^3 = H	−0.3	A	**5**	36
6	R^1 = CH_3 R^2, R^3 = H	4.5	C	**6**	51
7	R^2 = OCH_3 R^1, R^3 = H	4.2	C	**7**	92[c]
8	R^1, R^2, R^3 = H	4.7	B	**8**	79
9	R^1 = OCH_3 R^2, R^3 = H	4.5	C	**9**	49
10	R^3 = OCH_3 R^1, R^2 = H	5.4	C	**10**	47
11	R^3 = CH_3 R^1, R^2 = H	5.1	C	**11**	58
12	R^3 = F R^1, R^2 = H	4.7	B	**12**	98

[a] See Experimental Section for details. [b] Of chromatographically purified material except where indicated. [c] Isolated as a mixture containing 14% of a ring-alkylated isomer.

Table 2. Reaction Profile for the *tert*-Butylation of 2-Fluoroaniline

time (h)	% conversion at 90 °C[a]	% conversion at 110 °C[a]
2	29.2	66.4
4	37.3	83.1
8	48.0	90.0
12	59.2	93.0
20	75.5	96.1
68	89.6	97.4

[a] HPLC data. Starting material and expected product account for >97% of the material at all time points.

the *N-tert*-butylanilines can sometimes be isolated as their hydrobromide salts by crystallization directly from the reaction mixture upon cooling when method A or B is used.

Several acids, both organic and inorganic, were screened when the catalyst was selected. Mineral acids resulted in the cleanest reactions. Aqueous HCl worked well when *tert*-butyl alcohol was used as the *tert*-butyl cation source, but HCl-catalyzed method A reactions tended to stall when using isobutylene, presumably because of essentially irreversible removal of catalyst as *tert*-butyl chloride at relatively low temperature. Isobutylene is preferred over *tert*-butyl alcohol as the cation source because of the smaller amount of water present in the system at equilibrium.

The key to the success of the method is the high solubility of the substrates in the prescribed reaction mixture. For those substrates with low pK_a's (4 or under), the reaction mixtures are normally homogeneous under the stated conditions. Reactions of more basic substrates may be heterogeneous. Although 1,4-dioxane was the most generally useful cosolvent employed, other ethereal solvents such as 1,2-dimethoxyethane appear to be acceptable substitutes in certain cases and should be considered for large preparations.[4] Solvents containing an acyl residue (ethyl acetate, DMF, acetic acid) allowed competitive acylation of the anilines. The small amount of water introduced with the HBr proved essential to keep the anilinium salts solubilized. However, larger amounts of water were detrimental to the desired chemistry because of competition with the substrate for isobutylene that drives the equilibrium between starting material and product back toward starting material.

(1) Hickinbottom, W. J. *J. Chem. Soc., Part II* **1935**, 1279–1282.
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(4) Ethereal solvents, including 1,4-dioxane, have occasionally been used in the synthesis of *tert*-butyl ethers and esters. See, for example: Olsen, R. K.; Ramassamy, K.; Emery, T. *J. Org. Chem.* **1984**, *49*, 3527–3534.

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In summary, we have developed a convenient method to generate *N-tert*-butyl aromatic amines in moderate to excellent yield directly from the corresponding primary amine and isobutylene.

Experimental Section

Method A. A 25-mL glass pressure tube was charged with about 1 g of the aromatic amine, 1.1 equiv of 48% HBr, and 6 mL of dioxane. The mixture was cooled in a dry ice/acetone bath, and 6 mL of condensed isobutylene was added. The tube was sealed and heated for up to 4 days with magnetic stirring at 90–110 °C. Upon cooling to 0 °C, the tube was opened, and the mixture was partitioned between MTBE and aqueous NaOH. The organic layer was dried over Na_2SO_4 and concentrated. The product was purified by silica gel chromatography.

Method B. A 25-mL glass pressure tube was charged with about 1 g of the appropriate substrate, 0.6 mmol equiv of 48% HBr, and 6 mL of dioxane. The mixture was cooled in a dry ice/acetone bath, and 6 mL of condensed isobutylene was added. The tube was sealed and heated for 4–6 days at 140 °C. Reaction workup and product isolation were done in the same manner as method A.

Method C. A 25-mL glass pressure tube was charged with 1 g of the appropriate substrate, 1 equiv of 48% HBr, 1 equiv of pyridine, and 6 mL of dioxane. The mixture was cooled in a dry ice/acetone bath, and 6 mL of condensed isobutylene was added. The tube was sealed and heated for 3–5 days at 140 °C. The workup was done in the same manner as in method A.

***N-tert*-Butyl-2-chloroaniline (1).**[2] Method A, 110 °C, 3 days, obtained 1.15 g (78%). ^{1}H NMR ($CDCl_3$): 7.14 (d, 1H), 6.97 (t, 1H), 6.86 (d, 1H), 6.52 (t, 1H), 4.21 (s, 1H), 1.31 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$): 142.9, 129.3, 127.2, 120.9, 117.3, 115.0, 51.4, 29.9 ppm. IR (neat): 3419, 2927, 1740, 1598, 1515, 1466, 1326, 1218, 1038, 739 cm^{-1}.

***N-tert*-Butyl-4-chloroaniline (2).**[5] Method A, 110 °C, 4 days, obtained 1.06 g (74%). ^{1}H NMR ($CDCl_3$): 7.09 (d, 2H), 6.65 (d, 2H), 1.31 (s, 9H) ppm. ^{13}C NMR (CDCl3): 152.4, 137.2, 126.2, 112.8, 51.7, 29.4 ppm. IR (neat): 3417, 2975, 1598, 1493, 1393, 1366, 1320, 1258, 1094, 813, 685 cm^{-1}.

***N-tert*-Butyl-2-fluoroaniline (3).**[6] Method A, 110 °C, 3 days, obtained 1.09 g (81%). ^{1}H NMR ($CDCl_3$): 6.97 (m, 3H), 6.66 (m, 1H), 1.35 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$): 153.3 (d, J_{C1-F} = 236.9 Hz), 135.1 (d, J_{C2-F} = 11.3 Hz), 123.9 (d, J_{C3-F} = 3.0 Hz), 117.7 (d, J_{C5-F} = 7.5 Hz), 117.5, 114.6 (d, J_{C6-F} = 20.3 Hz), 51.5, 29.9 ppm. IR (neat): 3433, 2973, 2858, 2684, 1619, 1515, 1254, 1221, 1121, 1067, 911, 874, 741 cm^{-1}.

***N-tert*-Butyl-4-nitroaniline (4).**[7] Method A, 110 °C, 18 h, obtained 1.13 g (80%) as a yellow solid. Mp: 68.5–70.0 °C. ^{1}H NMR ($CDCl_3$): 8.03 (d, 2H), 6.55 (d, 2H), 4.64 (s, 1H), 1.43 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$): 152.4, 137.2, 126.2, 112.8, 51.7, 29.4 ppm. IR (mull): 2968, 2929, 2856, 1600, 1461, 1329, 1187, 1067, 909 cm^{-1}.

***N-tert*-Butyl-2-nitroaniline (5).**[8] Method A, 110 °C, 18 h, obtained 0.42 g (30%). ^{1}H NMR ($CDCl_3$): 8.40 (s, 1H), 8.17 (d, 1H), 7.35 (t, 1H), 7.10 (d, 1H), 6.59 (t, 1H), 1.50 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$): 145.0, 135.3, 132.4, 127.3, 115.9, 114.6, 51.6, 29.7 ppm. IR (neat): 3357, 2981, 1621, 1609, 1490, 1439, 1275, 1191, 1156, 1040, 736 cm^{-1}.

***N-tert*-Butyl-2-methylaniline (6).**[5] Method C, 4 days, obtained 0.78 g (51%). ^{1}H NMR ($CDCl_3$): 7.05 (m, 2H), 6.90 (d, 1H), 6.62 (m, 1H), 2.11 (s, 3H), 1.38 (s, 9H). ^{13}C NMR ($CDCl_3$): 145.0, 130.4, 126.6, 123.6, 117.1, 114.2, 51.91, 30.2, 18.1 ppm. IR (neat): 3440, 2971, 2871, 1740, 1607, 1515, 1482, 1366, 1318, 1264, 1227, 1212, 1055, 743 cm^{-1}.

***N-tert*-Butyl-3-methoxyaniline (7).**[9] Method C, 4 days, obtained 1.36 g (92%) as a mixture containing 14% of a ring-alkylated isomer. ^{1}H NMR ($CDCl_3$): 6.96 (t, 1H), 6.23 (m, 3H), 3.70 (s, 3H), 1.25 (s, 9H). ^{13}C NMR ($CDCl_3$): 171.1, 160.4, 148.2, 129.5, 110.1, 102.9, 51.4, 30.0 ppm. IR (neat): 3402, 2966, 1737, 1613, 1218, 1160, 1046, 753 cm^{-1}.

***N-tert*-Butylaniline (8).** Method C, 5 days, obtained 1.05 g (79%). ^{1}H NMR ($CDCl_3$): 7.14 (t, 2H), 6.74 (m, 3H), 1.30 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$): 146.9, 128.9, 118.3, 117.5, 51.4, 30.1 ppm. IR (neat): 3042, 2971, 1737, 1602, 1499, 1221, 1046, 743 cm^{-1}.

***N-tert*-Butyl-2-methoxyaniline (9).**[5] Method C, 4 days, obtained (49%). ^{1}H NMR ($CDCl_3$): 6.38 (m, 4H), 3.80 (s, 3H), 1.36 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$): 148.1, 136.7, 120.7, 116.8, 114.4, 109.7, 55.4, 29.9 ppm. IR (neat): 3425, 2968, 1740, 1603, 1482, 1364, 1258, 1177, 1119, 1028, 739 cm^{-1}.

***N-tert*-Butyl-4-methoxyaniline (10).**[5] Method C, 4 days, obtained 0.69 g (47%). ^{1}H NMR ($CDCl_3$): 6.74 (s, 4H), 3.70 (s, 3H), 2.92 (s, 1H), 1.22 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$): 154.3, 139.7, 122.7, 113.9, 52.1, 30.0 ppm. IR (neat): 3388, 2964, 1739, 1506, 1455, 1389, 1219, 1121, 1040, 874, 801, 768 cm^{-1}.

***N-tert*-Butyl-4-methylaniline (11).**[5] Method C, 3 days, obtained 0.89 g (58%). ^{1}H NMR ($CDCl_3$): 6.97 (d, 2H), 6.70 (d, 2H), 2.22 (s, 3H), 1.28 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$): 144.2, 129.3 128.4, 119.1, 51.7, 30.1, 20.4. IR (neat): 3402, 2973, 2869, 1737, 1617, 1515, 1364, 1219, 1046, 809 cm^{-1}.

***N-tert*-Butyl-4-fluoroaniline (12).**[10] Method B, 5 days, obtained 0.91 g (98%). ^{1}H NMR ($CDCl_3$): 6.91 (m, 2H), 6.74 (m, 2H), 1.26 (m, 9H). ^{13}C NMR ($CDCl_3$): 157.3 (d, J_{C1-F} = 238 Hz), 142.7, 120.7 (d, J_{C2-F} = 6.8 Hz), 115.2 (d, J_{C3-F} = 22 Hz), 52.0, 30.0. IR (neat): 3417, 2973, 1711, 1615, 1507, 1391, 1218, 820, 780, 685 cm^{-1}.

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