Studies on Selective Preparation of Aromatic Compounds. Part 16.[1] A Convenient Preparation of 1,2-Di- and 1,2,3-Tri-substituted Benzenes using the t-Butyl Function as a Positional Protective Group

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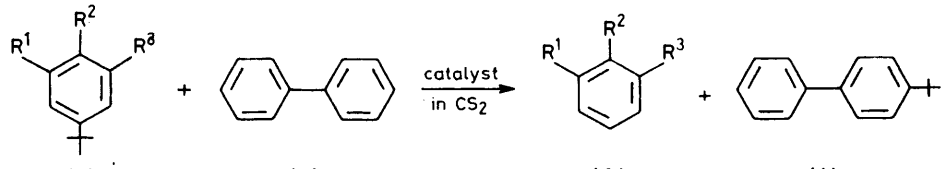
Some 1,2-disubstituted benzenes (3a, d—g, and j—m) and 1,2,3-trisubstituted benzenes (3b, c, h, and i) have been prepared by the Lewis acid catalysed trans-t-butylation of the corresponding t-butyl derivatives (1a—m) in the presence of biphenyl used as an acceptor for the t-butyl group.

It has been previously reported that the t-butyl group can serve as a positional protective group for the preparation of halogenophenols,[2] alkylphenols,[3] hydroxybiphenyls,[4] hydroxydiphenylmethanes,[5,6] and 2,2'-disubstituted diphenylalkanes.[1] The formation of some 1,2-di- and 1,2,3-tri-substituted benzenes has been reported.[7-9] However, the reported methods seem not to be practical since the isolation of the desired products was very difficult. We now report a convenient method using biphenyl as an acceptor for the t-butyl group in the Lewis acid catalysed trans-t-butylation of some t-butylbenzene derivatives affording the desired 1,2-di- and 1,2,3-tri-substituted benzenes.

The Lewis acid catalysed trans-t-butylation of compounds (1a—m) was carried out in the presence of biphenyl (2) acting as an acceptor for the t-butyl group



(1) (2) (3) (4)

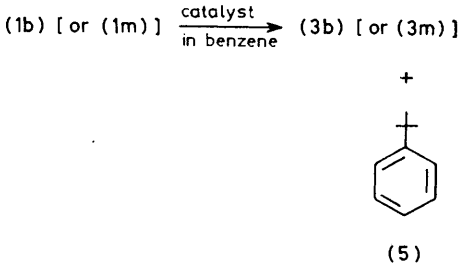
	R^1	R^2	R^3		R^1	R^2	R^3
a;	H	C_2H_5	CH_3	h;	CH_3	CH_3	Br
b;	CH_3	CH_3	CH_3	i;	CH_3	Br	CH_3
c;	CH_3	C_2H_5	CH_3	j;	H	F	Cl
d;	H	CH_3	Cl	k;	H	F	Br
e;	H	CH_3	Br	l;	H	Cl	Br
f;	H	C_2H_5	Cl	m;	H	Br	Br
g;	H	C_2H_5	Br				

Lewis acid catalysed trans-t-butylation of (1) [a]

Run	Substance	Catalyst [b]	Temp. (°C)	Product (isolated yield %)
1 [c]	(1a)	B	50	(3a) (73.3)
2 [d]	(1b)	B	50	(3b) (50), (5) (50)
3 [c]	(1b)	B	50	(3b) (88)
4 [c]	(1c)	B	50	(3c) (69)
5	(1d)	A	15	(3d) (80)
6	(1e)	A	15	(3e) (90)
7	(1f)	A	15	(3f) (82)
8	(1g)	A	15	(3g) (88)
9	(1h)	A	15	(3h) (79)
10	(1i)	A	15	(3i) (80)
11 [e]	(1j)	A	20	No reaction
12 [e]	(1k)	A	20	(3k) (64)
13 [e]	(1l)	A	20	(3l) (74)
14 [d]	(1m)	A	50	(3m) (50), (5) (50)
15 [d,e]	(1m)	A	20	(3m) (12), (6) (17), (7) (5), (4) (60)

[a] Reaction time, 1 h; [biphenyl] : [(1)] 5 : 1; [catalyst] : [(1)] 0.2; solvent CS_2 unless otherwise indicated. [b] A, $AlCl_3$; B, $AlCl_3$–CH_3NO_2. [c] Solvent CCl_4. [d] Benzene was used as solvent and acceptor. The relative yields of products were determined by g.l.c. [e] Reaction time 5 h.

As are shown in runs 2 and 14 of the Table, the formation of the expected (3b and m) was observed for $AlCl_3$–CH_3NO_2 and $AlCl_3$ catalysed trans-t-butylation of (1b and m) wherein benzene was used as both solvent and acceptor. However, the isolation of (3b and m) from



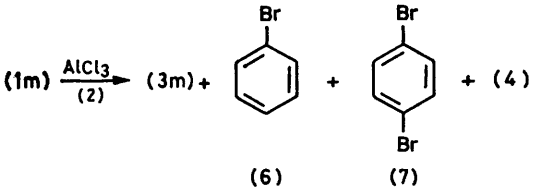
(5)

the reaction mixture by distillation was very difficult since the b.p.s of these compounds are almost the same as that of t-butylbenzene (5). These results suggest clearly that benzene is not a suitable acceptor for the preparation of 1,2-di- and 1,2,3-tri-substituted benzenes which have almost the same b.p.s as that of (5).

During trans-t-butylation using (2) in place of benzene as an acceptor, the desired 1,2-di- and 1,2,3-tri-substituted benzenes (3a—i, k, l) could easily be isolated by distillation in good yields. The formation of 4-t-butyldiphenyl (4) was determined by g.l.c. analysis but not isolated.

It was found in the trans-t-butylation of alkyl-halogeno- (1d—i) and dihalogeno-t-butylbenzenes (1j—m) that $AlCl_3$–CH_3NO_2 was a less active catalyst than $AlCl_3$, and did not catalyse the transalkylation of t-butyl-benzenes containing halogen atoms.

However, during $AlCl_3$ catalysed trans-t-butylation of (1j), the expected (3j) was not isolated. It was also



found that the $AlCl_3$ catalysed trans-t-butylation of (1m) in the presence of (2) afforded bromobenzene (6) and *p*-dibromobenzene (7) besides the desired (3m). This result suggests that transbromination took place together with trans-t-butylation.

Based on the results we conclude that our method using (2) as an acceptor is more convenient than those reported.[7-9] Unfortunately there are some limitations in the preparation of dihalogenobenzenes such as (3j and m).

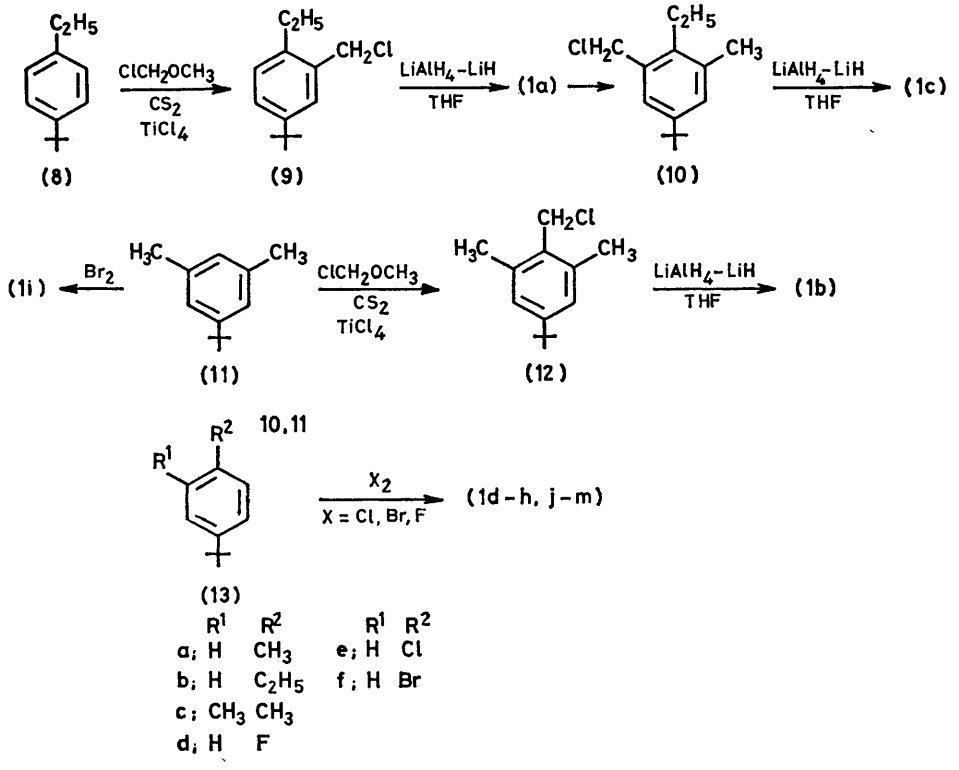
The starting materials were prepared as in the Scheme.

EXPERIMENTAL

M.p.s and b.p.s are uncorrected. I.r. spectra were measured as KBr pellets or liquid films on NaCl plates on a Nippon Bunko i.r. spectrophotometer and n.m.r. spectra were determined at 60 MHz with a Hitachi R-20 n.m.r. spectrometer with Me_4Si as internal reference.

Analytical Procedure.—Analyses were carried out by g.l.c. using a Yanagimoto Yanaco YR-101 gas chromatograph, 30% high vacuum silicon grease, 2 m, rate of increase of column temperature 12 °C min^{-1}; carrier gas, helium, 50 ml min^{-1}.

Preparation of 2-Ethyl-5-t-butylbenzyl Chloride (9).—To a solution of ethyl-4-t-butylbenzene (8) (100 g, 616 mmol) [10] and $ClCH_2OCH_3$ (99.2 g, 1 232 mmol) in CS_2 (300 ml) was added $TiCl_4$ (28 ml, 140 mmol). After the mixture was stirred at −5 °C for 2 h, it was poured into ice–water (500 ml). The organic layer was separated and the water layer was extracted with ether. The combined solutions were dried (Na_2SO_4) and evaporated *in vacuo* to leave a residue which was distilled under reduced pressure to afford starting material (27.3 g) and (9) (80.9 g, 62.4%), b.p. 102—103 °C at 3 mmHg; $\nu_{max.}$(NaOH) 2 960, 1 500, 1 460, 1 375, 1 257, 840, and 700 cm^{-1}; $\delta(CCl_4)$ 1.30 [9 H, s, $(CH_3)_3$], 1.24 (3 H, t, CH_3, *J* 8 Hz), 2.70 (2 H, q, CH_2, *J* 8 Hz), 4.51 (2 H, s, CH_2Cl), and 7.10—7.30 (3 H, m, ArH) (Found: C, 74.0; H, 9.1. $C_{13}H_{19}Cl$ requires C, 74.1; H, 9.1%).



SCHEME

Preparation of 1-*Ethyl*-2-*methyl*-4-*t*-*butylbenzene* (1a).—A mixture of $LiAlH_4$ (1.23 g, 33 mmol), LiH (2.98 g, 375 mmol), and THF (75 ml) was refluxed for a few minutes. To the solution (9) (49 g, 228 mmol) was added gradually over 40 min. The mixture was refluxed for 1 h and cooled to 10 °C. To the mixture, kept below 20 °C, was added THF–water (25 ml; 60 : 40 v/v), and the whole poured into dilute H_2SO_4 (25 ml; 1 : 1) and extracted with ether. The ethereal solution was dried (Na_2SO_4) and evaporated *in vacuo* to leave a residue which was distilled under reduced pressure to afford (1) (39 g, 98%), b.p. 71—72 °C at 3 mmHg; δ(CCl_4) 1.15 (3 H, t, CH_3, *J* 8 Hz), 1.27 [9 H, s, $(CH_3)_3$], 2.50 (3 H, s, CH_3), 2.55 (2 H, q, CH_2, *J* 8 Hz), and 6.95—7.10 (3 H, m, ArH) (Found: C, 88.25; H, 11.4. $C_{13}H_{20}$ requires C, 88.55; H, 11.45%).

Preparation of 2-*Ethyl*-3-*methyl*-5-*t*-*butylbenzyl Chloride* (10).—Similarly, (1a) (17.6 g, 100 mmol) was treated with $ClCH_2OCH_3$ in the presence of $TiCl_4$ as described above to afford (10) (15.5 g, 69%), b.p. 113—114 °C at 3 mmHg; δ(CCl_4) 1.15 (3 H, t, CH_3, *J* 8 Hz), 1.29 [9 H, s, $(CH_3)_3$], 2.30 (3 H, s, CH_3), 2.70 (2 H, q, CH_2, *J* 8 Hz), 4.50 (2 H, s, CH_2Cl), and 7.04 (2 H, s, ArH) (Found: C, 74.75; H, 9.4. $C_{14}H_{21}Cl$ requires C, 74.8; H, 9.4%).

Preparation of 4-*Ethyl*-3,5-*dimethyl*-1-*t*-*butylbenzene* (1c).—A mixture of (10) (11.25 g, 50 mmol), $LiAlH_4$ (0.246 g, 6.5 mmol), and LiH (0.596 g, 75 mmol) in THF (25 ml) was treated as above to afford (1c) (9.37 g, 98.6%), b.p. 85—86 °C at 3 mmHg; $\nu_{max.}$(NaCl) 2 960, 1 480, 1 450, 1 360, and 870 cm^{-1}; δ(CCl_4) 1.08 (3 H, t, CH_3, *J* 8 Hz), 1.27 [9 H, s, $(CH_3)_3$], 2.27 (6 H, s, CH_3), 2.08 (2 H, q, CH_2, *J* 8 Hz), and 6.88 (2 H, s, ArH) (Found: C, 88.05; H, 11.65. $C_{14}H_{22}$ requires C, 88.35; H, 11.65%).

Preparation of 4-*Chloromethyl*-3,5-*dimethyl*-1-*t*-*butylbenzene* (12).—A solution of 5-t-butyl-*m*-xylene (50 g, 308 mmol) [11] and $ClCH_2OCH_3$ (49.6 g, 616 mmol) in CS_2 (150 ml) was treated with $TiCl_4$ (14 ml) and worked up as described above to give (12) (60.54 g, 93.3%), b.p. 95—97 °C at 3 mmHg (lit.,[7] 124 °C at 6 mmHg); $\nu_{max.}$(NaCl) 2 960, 1 460, 1 260, 1 240, 870, 730, and 680 cm^{-1}; δ($CDCl_3$) 1.30 [9 H, s, $(CH_3)_3$], 2.41 (6 H, s, CH_3), 4.62 (2 H, s, CH_2), and 7.07 (2 H, s, ArH). A small amount of 2,2′,6,6′-*tetramethyl*-4,4′-*di*-*t*-*butyldiphenylmethane* (4.1%) was obtained as a by-product, m.p. 135—136 °C, needles (from EtOH); $\nu_{max.}$(KBr) 2 960, 1 600, 1 480, 1 360, 1 300, 1 240, 1 200, 875, and 720 cm^{-1}; δ($CDCl_3$) 1.30 [18 H, s, $(CH_3)_6$], 2.14 (12 H, s, 4 × CH_3), 4.02 (2 H, s, CH_2), and 6.98 (4 H, s, ArH) (Found: C, 89.2; H, 10.7. $C_{25}H_{36}$ requires C, 89.2; H, 10.8%).

Preparation of 3,4,5-*Trimethyl*-1-*t*-*butylbenzene* (1b).—Reduction of (12) was carried out as described above to afford (1b) in 94.3% yield, needles (from EtOH), m.p. 30—31 °C (lit.,[7] 30—32 °C); $\nu_{max.}$(NaCl) 2 960, 1 480, 1 360, 1 230, 1 200, 865, and 715 cm^{-1}; δ(CCl_4) 1.29 [9 H, s, $(CH_3)_3$], 2.10 (3 H, s, CH_3), 2.16 (6 H, s, CH_3), and 7.02 (2 H, s, ArH).

Preparation of 3-*Chloro*-4-*methyl*-1-*t*-*butylbenzene* (1d).—To a mixture of (13a) (29.6 g, 200 mmol) and a small amount of iron powder in CCl_4 (60 ml) was slowly added chlorine gas at 5—8 °C over 3 h. The mixture was poured into a large amount of ice–water. The organic layer was separated and the water layer extracted with ether. The combined solutions were dried (Na_2SO_4) and evaporated *in vacuo* to leave a residue which was distilled under reduced pressure affording (1d) (30.2 g, 82.7%), b.p. 59—62 °C at 3 mmHg; $\nu_{max.}$(NaCl) 2 960, 1 480, 1 260, 1 120, 1 050, 870, 815, and 810 cm^{-1}; δ(CCl_4) 1.27 [9 H, s, $(CH_3)_3$], 2.29 (3 H, s, CH_3), and 7.00—7.31 (3 H, m, ArH) (Found: C, 72.45; H, 8.3. $C_{11}H_{15}Cl$ requires C, 72.3; H, 8.3%).

Preparation of 3-*Bromo*-4-*methyl*-1-*t*-*butylbenzene* (1e).—To a solution of (13a) (29.65 g, 200 ml) in CCl_4 (20 ml) in the presence of a small amount of iron powder was added a solution of bromine (35.2 g, 220 mmol) in CCl_4 (15 ml) at 5 °C over 20 min. After the mixture was stirred at 15 °C for 2 h, it was treated as above to afford (1e) (40.3 g, 88.6%), b.p. 79—80 °C at 3 mmHg; $\nu_{max.}$(NaCl) 2 960, 1 495, 1 260, 1 045, and 820 cm^{-1}; δ(CCl_4) 1.25 [9 H, s, $(CH_3)_3$], 2.30 (3 H, s, CH_3), and 7.04—7.43 (3 H, m, ArH) (Found: C, 58.15; H, 6.6. $C_{11}H_{15}Br$ requires C, 58.15; H, 6.65%).

Preparation of 3-*Chloro*-4-*ethyl*-1-*t*-*butylbenzene* (1f).—Similarly, chlorination of (13b) [10] was carried out as described above to afford (1f) in 73.2% yield, b.p. 70—73 °C at 3 mmHg; $\nu_{max.}$(NaCl) 2 960, 1 480, 1 460, 1 385, 1 260, and 870 cm^{-1}; δ(CCl_4) 1.18 (3 H, t, CH_3, *J* 8 Hz), 1.35 [9 H, s, $(CH_3)_3$], 2.67 (2 H, q, CH_2, *J* 8 Hz), and 7.12—7.39 (3 H, m, ArH) (Found: C, 73.5; H, 8.35. $C_{12}H_{17}Cl$ requires C, 73.25; H, 8.7%).

Preparation of 3-*Bromo*-4-*ethyl*-1-*t*-*butylbenzene* (1g).—Similarly, bromination of (13b) gave (1g) in 86.3% yield, b.p. 85—°6 °C at 3 mmHg (lit.,[9] 77 °C at 0.5 mmHg); $\nu_{max.}$(NaCl) 2 960, 1 475, 1 450, 1 260, 1 120, 1 040, and 825 cm^{-1}; δ(CCl_4) 1.24 [9 H, s, $(CH_3)_3$], 1.26 (3 H, t, CH_3, *J* 8 Hz), 2.65 (2 H, q, CH_2, *J* 8 Hz), and 7.00—7.45 (3 H, m, ArH).

Preparation of 3-*Bromo*-4,5-*dimethyl*-1-*t*-*butylbenzene* (1h).—Similarly, bromination of (13c) [10] afforded (1h) in 95% yield, b.p. 94—95 °C at 3 mmHg; $\nu_{max.}$(NaCl) 2960, 1480, 1 290, 1 050, and 875 cm^{-1}; δ(CCl_4) 1.22 [9 H, s, $(CH_3)_3$], 2.33 (6 H, s, CH_3), and 6.90—7.33 (2 H, m, ArH) (Found: C, 60.15; H, 7.15. $C_{12}H_{17}Br$ requires C, 59.75; H, 7.1%).

Preparation of 4-*Bromo*-3,5-*dimethyl*-1-*t*-*butylbenzene* (1i).—Similarly, bromination of (11) [10] gave (1i) in 95.3% yield, m.p. 47—48 °C (EtOH); $\nu_{max.}$(KBr) 2 960, 1 460, 1 240, 1 040, 1 020, 870, and 720 cm^{-1}; δ(CCl_4) 1.25 [9 H, s, $(CH_3)_3$], 2.37 (6 H, s, CH_3), and 6.98 (2 H, s, ArH) (Found: C, 59.9; H, 7.15%).

Preparation of 3-*Chloro*-4-*fluoro*-1-*t*-*butylbenzene* (1j).—Similarly, chlorination of (13d) [11] afforded (1j) in 72% yield, b.p. 91—93 °C at 15 mmHg; $\nu_{max.}$(NaCl) 2 950, 1 570, 1 450, 1 250, 1 200, 1 040, 860, and 800 cm^{-1}; δ(CCl_4) 1.37 [9 H, s, $(CH_3)_3$] and 7.36—7.80 (3 H, m, ArH) (Found: C, 64.7; H, 6.6. $C_{10}H_{12}ClF$ requires C, 64.35; H, 6.5%).

Preparation of 3-*Bromo*-4-*fluoro*-1-*t*-*butylbenzene* (1k).—Similarly, bromination of (13d) gave (1k) in 80% yield, b.p. 62—63 °C at 3 mmHg; $\nu_{max.}$(NaCl) 2 960, 1 570, 1 480, 1 400, 1 260, 925, 870, and 815 cm^{-1}; δ(CCl_4) 1.27 [9 H, s, $(CH_3)_3$] and 6.85—7.55 (3 H, m, ArH) (Found: C, 52.05; H, 5.35. $C_{10}H_{12}BrF$ requires C, 51.95; H, 5.25%).

Preparation of 3-*Bromo*-4-*chloro*-1-*t*-*butylbenzene* (1l).—Similarly, bromination of (13e) [11] afforded (1l) in 74.1% yield, b.p. 82—83 °C at 3 mmHg; $\nu_{max.}$(NaCl) 2 960, 1 470, 1 455, 1 375, 1 020, and 820 cm^{-1}; δ(CCl_4) 1.28 [9 H, s, $(CH_3)_3$] and 7.18—7.56 (3 H, m, ArH) (Found: C, 48.1; H, 4.65. $C_{10}H_{12}BrCl$ requires C, 48.51; H, 4.9%).

Preparation of 3,4-*Dibromo*-1-*t*-*butylbenzene* (1m).—Similarly, bromination of (13f) [11] gave (1m) in 82.1% yield, b.p. 107—108 °C at 3 mmHg; $\nu_{max.}$(NaCl) 2 950, 1 465, 1 450, 1 365, 1 010, and 810 cm^{-1}; δ(CCl_4) 1.29 [9 H, s, $(CH_3)_3$] and 6.98—7.56 (3 H, m, ArH) (Found: C, 74.0; H, 9.1. $C_{10}H_{12}Br_2$ requires C, 41.15; H, 4.15%).

Typical Procedure for Trans-t-butylation.—To a solution

of (1a) (8.8 g, 50 mmol) and biphenyl (38.55 g, 250 mmol) in CCl_4 (100 ml) was added a solution of aluminium chloride (1.32 g, 10 mmol) in nitromethane (2.5 ml) at 50 °C. The mixture was stirred at 50 °C for 2 h, quenched with a large amount of ice–water, and extracted with ether. The ethereal solution was washed with a small amount of water, dried (Na_2SO_4), and evaporated *in vacuo* to leave a residue which was distilled under reduced pressure to afford 2-ethyltoluene (3a) (4.4 g, 73.3%), b.p. 63—65 °C at 13 mmHg (lit.,[12] b.p. 62—63 °C at 20—21 mmHg). The yields in other cases are shown in the Table: (3b), b.p. 64—66 °C at 13 mmHg (lit.,[7] 176.1—176.2 °C); (3c), b.p. 79—80 °C at 13 mmHg (lit.,[7] 189—190 °C); (3d), b.p. 55—57 °C at 15 mmHg (lit.,[13] 155—158 °C); (3e), b.p. 74—76 °C at 13 mmHg (lit.,[14] 178—181 °C); (3f), b.p. 68—71 °C at 13 mmHg (lit.,[15] 178.5 °C); (3g), b.p. 90—91 °C at 13 mmHg (lit.,[16] 202—204 °C); (3h), b.p. 104—105 °C at 13 mmHg (lit.,[17] 211.3—211.6 °C); (3i) b.p. 89—90 °C at 15 mmHg (lit.,[18] 206 °C); (3k), b.p. 52—54 °C at 13 mmHg (lit.,[19] 57 °C at 22 mmHg); (3l), b.p. 85—87 °C at 13 mmHg (lit.,[20] 204 °C).

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