Preparation of 1,3,5-Tris(aminomethyl)-2,4,6-triethylbenzene from Two Versatile 1,3,5-Tri(halosubstituted) 2,4,6-Triethylbenzene Derivatives

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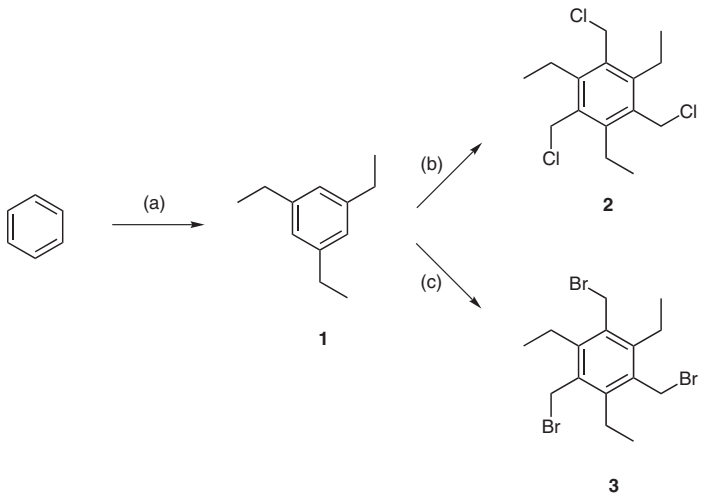
Abstract: The use of 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene and the intermediates 1,3,5-tris(halomethyl)-2,4,6-triethylbenzene (halo = bromo and chloro) compounds, have been utilized as scaffolds for many molecular receptors. We report here for the first time a detailed practical synthetic procedure, starting from benzene, and in four straightforward steps, to prepare 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene, a very versatile molecular scaffold. The added advantage is the limited chromatography in the purification procedure.

Key words: molecular receptors, pinwheel, substituted aromatic alkyl halides, Staudinger reduction, triethylbenzene scaffold



Scheme 1 (a) $AlCl_3$, EtBr, 0 °C to r.t.; (b) CS_2, $ClCH_2OMe$, 25 °C; (c) 33% HBr in AcOH, Zn, $(CH_2O)_n$, 90 °C.

Introduction

The use of benzene-derived compounds as scaffolds has played an important role in host-guest recognition and has been recently reviewed.[1–4] The concept and ability to utilize hexa-substituted benzene for preorganization has been known since 1975 by MacNicol[5,6] and has been used extensively by many research groups including our own.[7,8]

The present paper describes the full synthesis of 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene (**5**) starting from benzene. As the synthesis of benzene-derived scaffolds has become important over recent years, a simple synthetic route has been refined for the preparation of such systems. 1,3,5-Triethylbenzene is commercially available, however, it is relatively expensive whereas benzene is inexpensive and can be easily converted to 1,3,5-triethylbenzene in high yields as described in the experimental section.

Scope and Limitations

One of the most interesting chemical aspects of the synthesis of 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene scaffolds is the initial synthesis of 1,3,5-triethylbenzene (**1**). Conventional chemistry states that once benzene has

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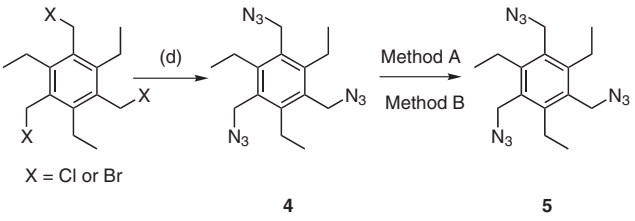
been alkylated, the ethyl substituent is *ortho-para* directing for further substitution, but this reaction gives ethyl groups *meta* to each other. The standard *ortho-para* directing arguments are based upon kinetic-control reasoning. However, with reversible reactions the product from thermodynamic control can dominate. *Meta* substitution is thermodynamically favored because of lower steric strain than *ortho* substitution, which results in a good yield of 1,3,5-triethylbenzene (**1**) (Scheme 1).

The key step for the preparation of 1,3,5-substituted 2,4,6-triethylbenzene derivatives is the installation of three halomethyl groups into 1,3,5-triethylbenzene. To avoid low yields and cumbersome column chromatography, the use of the reported method[9] for the chloromethylation of durene has achieved good success for the similar reaction on triethylbenzene. Siegel et al. recently published a similar procedure for the same compound.[10] The following procedure has been optimized to obtain the trichloromethylated product in a single step, and has been accomplished on a 20 g scale with respect to the triethylbenzene starting reactant. Previous methods resulted in incomplete reaction requiring a second reaction to obtain the desired hexa-substituted product or column chromatography to separate the mono-, di- and tri-halomethylated products. The procedure described herein has been optimized such that only the trichloromethylated product is observed by ^{1}H NMR spectroscopy. It should be noted that TLC indicates that small amounts <1 g (20 g scale reaction) of mono- and dichloromethylated compounds have been detected in the methanol filtrate (*vide infra*). It is believed that tin(IV) chloride of high purity is the key for successful trichloromethylation without the use of large excesses of reagents. Aldrich tin(IV) chloride (99%) is of sufficient purity (>99% is not necessary) for use. Through the scale-up process, a significant obstacle to obtaining the desired product was a complete conversion. Temperature, order of reagent addition, and an inert atmosphere were determined to be important variables in avoiding a mixture of the di- and trichloromethylated products (TLC). It is interesting to note that the mono- and dichloromethylated products can be obtained selectively based only on stoichiometry, i.e. one equivalent of chloromethyl methyl ether, results in the preparation of the monochloromethylated product. While nine equivalents of chloromethyl methyl ether were required for complete conversion in earlier work, it has been subsequently determined that rapid, mechanical stirring (especially for scales larger than 5 g with respect to triethylbenzene) replaces the need for such a large excess. With such stirring, only a two-fold excess (six equivalents of chloromethyl methyl ether) is necessary for complete conversion in 80–90% average yields. An 87% yield of material of adequate purity by ^{1}H NMR spectroscopy was obtained on the scale above. Even though the synthesis of the 1,3,5-trischloro-2,4,6-triethylbenzene (**2**) has been improved, chloromethyl methyl ether is known to be highly carcinogenic. However the preparation of the 1,3,5-trisbromo-2,4,6-triethylbenzene (**3**) discovered independently by Walsdorff[11] and us[12] following a different approach outlined by van der Made[13] has been shown to be an alternative and attractive method for the preparation of the tris-amino compound.

The conversion of either the trischloride or trisbromide into the trisazide product was accomplished by dissolving the 1,3,5-trihalomethyl-2,4,6-triethylbenzene (halo = bromide or chloride) in dimethylformamide followed by adding 6 mole equivalents of sodium azide and stirring at room temperature. Reactions have proceeded well on a 10 g scale weight of trisazide. The reaction was stirred overnight and monitored by TLC. Solid sodium chloride and unreacted sodium azide were filtered over Celite, and the pad was rinsed with dichloromethane. Addition of dichloromethane to the dimethylformamide filtrate results in further precipitation of unreacted sodium azide, which was filtered once again.

Since the reduction of the azide groups into amines proceeds cleanly via Staudinger reduction, purification of the trisazide by recrystallization from ethyl acetate and hexanes has been found adequate to result in trisamine that requires no purification for subsequent use. For the recrystallization of the trisazide, the product was dissolved by adding a minimum amount of hot ethyl acetate, followed by adding hexanes (room temperature) until cloudiness just persists, cooling to room temperature then placing in a 0 °C freezer. Isolation of the product was accomplished through filtration. This product was subjected to a shock test by hitting approximately 100 mg on an anvil with a hammer. This was done to three different samples. Although none of these tests showed any shock sensitivity, one should always treat azide derivatives with the utmost care, and it is recommended that a blast shield is used when handling sodium azide. An alternative method for the reduction of azides to amines is hydrogenation. This procedure produces higher yields over the Staudinger reduction, however, an appropriate apparatus is required and care must be taken when carrying out the hydrogenation (Scheme 2).



Scheme 2 (d) NaN_3, DMF; Method A: Ph_3P, THF–H_2O (10:1); Method B: H_2, 10% Pd/C, absolute EtOH.

In summary, 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene (**5**) has been synthesized by four simple steps from 1,3,5-trisubstituted 2,4,6-triethylbenzene (trischloromethyl **2** or trisbromomethyl **3**). Relatively moderate to high yields for each synthetic step is obtained with the added advantage that very little chromatography is required. Due to health and safety reasons and ease of preparation, the route carried out by the authors is via the 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene (**3**), then converted to the azide **4** (Scheme2, Method B), followed by hydroge-

nation of the azide to the free amine **5**. The inclusion of the other routes is to highlight the ease of the synthetic route over the last couple of decades.

1,3,5-Triethylbenzene (1)

$AlCl_3$ (45.3 g, 340 mmol) was placed into an oven-dried, 250 mL three-necked round bottom flask equipped with a magnetic stir bar that was fitted with a reflux condenser and addition funnel. A N_2 balloon was attached to exclude atmospheric water. The water condenser was fitted with a tube that is submerged into an aq sat. solution of $NaHCO_3$ to quench the evolved HBr/HCl gas (Note 1). The reaction flask was cooled to 0 °C in an ice water bath. EtBr (50 mL, 590 mmol) was poured into the addition funnel and slowly added to the $AlCl_3$ with continuous stirring (Note 2). Once the addition of EtBr was complete, benzene (28.6 mL, 320 mmol) was added slowly over 20 min (Note 3). Once the addition of benzene had been completed, and the effervescence had ceased, EtBr (32.5 mL, 390 mmol) was then added dropwise whilst maintaining a reaction temperature of 0 °C. The reaction was stirred for 12 h allowing the mixture to warm to r.t. On completion, the mixture was decanted into a 1 L beaker containing ice, and once the ice had melted the pH of the aqueous layer was measured (Note 4). The mixture was extracted with Et_2O (250 mL) in a 1 L separating funnel (Note 5). The organic layer was separated, and the aqueous phase was extracted with Et_2O (2×100 mL). The organic phases were combined and washed as follows: H_2O (1×100 mL), aq 1 N NaOH (1×100 mL), and H_2O (1×100 mL). The organic phase was dried ($MgSO_4$), and filtered through Celite into a one-necked round bottom flask. The solvent was removed under reduced pressure, yielding a yellow oil. Upon vacuum distillation, a colorless oil was produced (Note 6); typical yields ranged from 80–90%. 1,3,5-Triethylbenzene (**1**) is a commercially available compound, and the spectral data were in agreement with those of the commercial source.

1,3,5-Tris(chloromethyl)-2,4,6-triethylbenzene (2)

CAUTION! Chloromethyl methyl ether is volatile and reported to be a potent carcinogen.

To a three-necked round-bottomed flask fitted with a mechanical stirrer, an efficient water condenser, and a pressure-equilibrating addition funnel, was added CS_2 (100 mL, 13 mmol) followed by 1,3,5-triethylbenzene (**1**; 13.4 mL, 123 mmol), which had been freshly distilled with a Kugelrohr apparatus at 65 °C/1 Torr. The solution was purged, by forcing dry N_2 through a glass dispersion tube submerged beneath the surface of the solvent for 15 min. Removal of dissolved O_2 from the solvent and subsequent inert reaction conditions are believed to minimize the color and impurities in the product. Following this step, $SnCl_4$ (43 mL, 652 mmol) (Note 7) was added resulting in the appearance of a bright yellow color. A $CaCl_2$ drying tube was also attached (Note 8). Chloromethyl methyl ether (64 mL, 1.1 mol), measured volumetrically with an appropriate-sized syringe, was added to the addition funnel, and the reaction was stirred on the fastest setting of the mechanical stirrer (Note 9). This reagent was added rapidly, allowing a controlled reflux resulting from the exothermicity of the reaction and the reaction was allowed to stir overnight (Note 10). For an in situ TLC analysis, a small aliquot was removed and washed with $NaHCO_3$. The organic layer was removed and dried ($MgSO_4$) before the TLC experiment was performed (Note 11). On completion of the reaction, the solution was carefully decanted over 500 g of ice. The reaction vessel was rinsed with CH_2Cl_2 (100 mL), and this was added to the CS_2/H_2O. Once all of the ice had melted, the aqueous and organic layers were separated, and the CS_2–CH_2Cl_2 was removed under reduced pressure (Note 12). The residue was dissolved in CH_2Cl_2 (250 mL) to which H_2O (50 mL) had been added. The mixture was decanted into a separating funnel, and the organic layer was separated, which was then washed with aq 1 N NaOH (100 mL), H_2O (100 mL), and brine (100 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (200 mL), and silica gel (100 g) was added to the flask. The suspension was shaken, and the CH_2Cl_2 was removed using a rotary evaporator. This solid mixture was loaded on a fritted filter, and washed repeatedly with 9:1 hexanes–CH_2Cl_2 until no more product was observed by TLC (cf. Note 12). The combined washes were evaporated in vacuo. The product was obtained as a white solid with ^1H and ^{13}C NMR spectra consistent with the desired compound;[10] mp 144 °C. Further purification has been accomplished through recrystallization from hot MeOH. Typical yields ranged from 80–90%. High temperature was not necessary for this reaction (Note 13).

^1H NMR ($CDCl_3$): δ = 1.31 (t, 9 H, *J* = 7.6 Hz), 2.93 (q, 6 H, *J* = 7.6 Hzz), 4.69 (s, 6 H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 16.0, 22.6, 40.6, 132.6, 145.0.[10]

1,3,5-Tris(bromomethyl)-2,4,6-triethylbenzene (3)

A water condenser was connected to a 250 mL oven-dried round-bottomed flask. Zn powder (5 g, 76 mmol) and AcOH (50 mL, 873 mmol) were added to the flask. HBr in AcOH (33% wt, 50 mL) was added slowly through the condenser over a 0.5 h period into the reaction vessel that was continuously stirred (Note 14). Once the HBr was added, the reaction mixture was stirred until the Zn had completely dissolved, and the solution turned into a clear tan/orange color. Triethylbenzene (**1**; 10 g, 62 mmol), paraformaldehyde (20 g), and HBr in AcOH (33% wt, 148 mL) were then added and the solution was heated to 90 °C for 48 h resulting in a dark brown solution (Note 15). The solution was allowed to cool slowly with continuous stirring, whence a white precipitate was formed over 2 h. The solid was filtered, washed with H_2O (3×100 mL), and allowed to dry under vacuum for 24 h (Note 16). Typical yields ranged from 60 to 70%; mp >150 °C (dec.).

^1H NMR ($CDCl_3$): δ = 1.34 (t, 9 H, *J* = 7.6 Hz), 2.94 (q, 6 H, *J* = 7.6 Hz), 4.58 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 15.6, 22.7, 28.5, 132.6, 145.0.

1,3,5-Tris(azidomethyl)-2,4,6-triethylbenzene (4)

CAUTION! NaN_3 has been found to be explosive under certain conditions and is highly toxic.

Method A: The conversion of the trihalo triethylbenzene (halo = chloro or bromo) into the trisazide product was achieved by dissolving either **2** or **3** in a mixture of DMF and CH_2Cl_2 (50 mL and 20 mL respectively), and heating the reaction mixture to 80 °C. A slurry of 6 mol equiv of NaN_3 was made up in distilled H_2O (20 mL), and added through the top of the condenser, which was subsequently rinsed with distilled H_2O and the reaction mixture was stirred gently for 22 h (Note 17). The condenser was removed from the flask whilst behind a blast shield (**Caution!** Note 18). The DMF was removed under reduced pressure, and distilled H_2O (100 mL) was added to the residue. The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (3×20 mL). The organic layers were combined, dried ($MgSO_4$), and filtered. The solvent was removed by rotary evaporation to afford an oil. The oil was purified by chromatography (Note 19) using EtOAc–*n*-hexane (25:75). The solvent was removed under reduced pressure to give a white solid; mp 61 °C.

IR (deposit from $CDCl_3$ on NaCl): 2084 cm^{-1} (N=N=N).[14]

^1H NMR ($CDCl_3$): δ = 1.23 (t, 9 H, *J* = 7.6 Hz), 2.85 (q, 6 H, *J* = 7.6 Hz), 4.49 (s, 6 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 15.7, 23.1, 47.9, 129.9, 145.0.

Method B: The conversation of trihalo triethylbenzene (halo = chloro or bromo) into 1,3,5-tris(azidomethyl)-2,4,6-triethylbenzene (**4**) has also been achieved by an alternative method whereby no chromatography is required. To a previously oven dried 500 mL round-bottomed flask, 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene (**3**; 10.8 g, 2.5 mmol) was added to DMF (250 mL) to

which NaN_3 (9.6 g, 14.8 mmol, 6 equiv) was added in small portions over 30 min and stirred at r.t. for 24 h. Any NaBr that precipitated was filtered through Celite. CH_2Cl_2 (200 mL) was added to the solution, which caused more NaBr to precipitate from the solution. This solution was filtered through Celite. The addition of CH_2Cl_2 was repeated until no further precipitate was observed; the solvent was then removed under reduced pressure. The residue was redissolved in CH_2Cl_2 (100 mL) and washed with H_2O (2 × 100 mL), then brine (1 × 100 mL), and dried ($MgSO_4$). The solvent removed under reduced pressure, and the product was recrystallized from EtOAc and *n*-hexane. Typical yields ranged from 70–80%. See Method A for the characteristic data.

1,3,5-Tris(aminomethyl)-2,4,6-triethylbenzene (5)

Method A: To the solid trisazide **4** (9.54 g, 29 mmol), was added Ph_3P (45.67 g, 174 mmol, 6 mol equiv), followed by a 10:1 solution of H_2O in THF (110 mL) (Note 20). For each gram of trisazide, 20 mL of THF was used with the appropriate ratio of H_2O. When the reaction was judged complete by TLC, the THF was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL), and washed twice with aq 1 N HCl (50 mL). The acidic aqueous phases were combined and extracted with EtOAc (4 × 50 mL) to remove any unreacted Ph_3P and the by-product Ph_3PO. The isolated acidic aqueous phase was carefully made alkaline by the addition of aq 3 N NaOH until the pH was ~10 as indicated by litmus paper. This solution was extracted with CH_2Cl_2 (3 × 70 mL), and the collected organic portions were dried ($MgSO_4$) and then evaporated under reduced pressure to isolate the product with typical yields ranging from 60–70%; mp 130–132 °C.

IR (KBr): 3359, 3291, 2965, 1585, 1044, 836 cm^{-1}.[14]

^1H NMR ($CDCl_3$): δ = 1.24 (t, 9 H, *J* = 7.6 Hz), 1.33 (br s, 6 H), 2.83 (q, 6 H, *J* = 7.6 Hz), 3.88 (s, 6 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 16.8, 22.5, 39.6, 137.4, 140.3.

Method B: The solid trisazide **4** (605 mg, 1.8 mmol) was dissolved in abs EtOH (35 mL) in a hydrogenation flask (pre-dried in the oven). Pd/C (10%, 61 mg) was added and the reaction mixture was stirred for 4 h at 30 mm/Hg. The Pd/C was filtered through two filter papers (Note 21) and the solvent was removed under reduced pressure. A pale yellow solid was obtained in yields exceeding 90%. See Method A for characterization data.

Notes

1. HCl and HBr are side products of the reaction and it is recommended that the acids be quenched using a base trap. The reaction should be carried out in a well-ventilated hood.

2. The EtBr was added over 30 min.

3. The addition of benzene results in an exothermic reaction. When a bicarbonate trap is used, bubbles should be observed as the acidic gases are quenched.

4. The aqueous layer should be acidic, and if not, 1 N HCl (100 mL) should be added carefully.

5. The beaker is rinsed with Et_2O to dissolve any residual product that has been left in the beaker and reaction vessel.

6. Short-path column chromatography with CH_2Cl_2 as eluent maybe necessary after distillation to remove any baseline impurity.

7. $SnCl_4$ (99%) was purchased from Aldrich and used as received. $SnCl_4$ is corrosive, therefore, gloves and adequate ventilation provided by a good fume hood is strongly advised.

8. This is only true when the Lewis acid is of sufficient purity.

9. Chloromethyl methyl ether is volatile and reported to be a potent carcinogen. Care should be taken to keep the temperature of this reagent below 0 °C while measuring it from the bottle.

10. For simplicity, the reaction was allowed to stir overnight, although the actual reaction is much faster and could probably be quenched as soon as the trichloromethylated product is observed by TLC.

11. A 10% solution of CH_2Cl_2 in hexanes is a good eluent for TLC on silica gel given that the starting material and the mono-, di-, and tri-substituted products are cleanly separated.

12. This should be carried out in a hood specifically designated for the removal of odoriferous compounds.

13. The heat generated is believed to help drive the reaction to completion.

14. Needs to be carried out in a well-ventilated hood as slight fuming may occur.

15. It is important that the temperature is maintained between 85–95 °C as it has been shown that a mixture of the mono- and disubstituted compounds are otherwise formed, and chromatography is required to separate the desired product.[11]

16. The filtrate was heated again to 90 °C and allowed to react for a further 24 h. This was repeated for a third time producing a final crop of the 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene.

17. Gentle stirring is recommended as this reduces the chance of NaN_3 splashing up in to the joints of the flask and the condenser from drying.

18. PTFE tape should be used around the joints. In our laboratory an explosion occurred when NaN_3 dried out in the joints when the condenser was removed from the flask because no PTFE tape was used. The removal of the condenser from the reaction vessel should be done behind a blast shield.

19. Preparative flash chromatography was performed on Scientific Adsorbents Incorporated Silica Gel 40 μm.

20. The 10:1 THF–H_2O solution is important to ensure complete reaction.

21. Pd/C is potentially pyrophoric when dry; hence the filter papers need to remain damp.

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