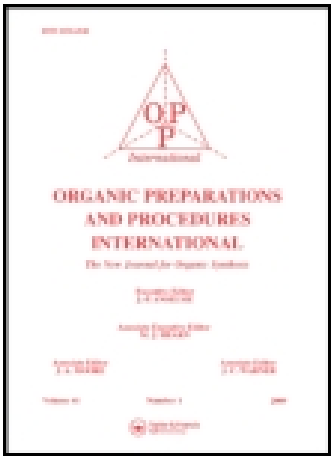

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New and Convenient Syntheses of 1-Amino-1-phenylbutane from n-Butylbenzene

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New and Convenient Syntheses of 1-Amino-1-phenylbutane from *n*-Butylbenzene

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n-Butylbenzene (**1**), an unwanted by-product formed in 10% yield during the manufacture of isobutylbenzene, has few industrial applications and is discarded by burning. In an attempt to produce a value-added product from **1**, we aimed at the synthesis of 1-amino-1-phenylbutane (**5**). 1-Amino-1-phenylbutane (**5**) is used as an intermediate for the synthesis of substituted triazoles,[1] aminothiazoles,[2] and a quinoline derivative which is a neurokinin-3 antagonist.[3] In its chiral form, **5** is useful as a resolving agent.[4] Because of its utility in biologically active molecules, we wanted to develop new synthetic routes to 1-amino-1-phenylbutane (**5**) starting from *n*-butylbenzene.

Racemic amine (**5**) had previously been prepared by: a) reduction of the oxime of butyrophenone with Ni, Na, Pd\C,[3] etc., b) the Leuckart reaction of butyrophenone,[5] c) reaction of propionitrile with phenylmagnesium bromide followed by reduction,[6] d) hydrolysis of the iminophosphorane of butyrophenone.[7] The chiral form of amine **5** was synthesized by: a) asymmetric reduction of ketimines using optically active alkoxylithium hydride[8] and ketoxime ethers with chiral oxazaborolidines,[9] b) asymmetric allylation of imines followed by reduction,[10] c) enantioselective synthesis *via* addition of Grignard reagent to chiral hydrazones,[11] d) asymmetric recognition by (R)-phenylglycyl-(R)-phenylglycine.[12] This paper reports three useful synthetic routes to compound **5** from *n*-butylbenzene.

In the first two methods, the bromination of (**1**) with NBS in CCl_4 under reflux conditions, gives α-bromophenylbutane (**2**). Although the reaction of (**2**) with potassium phthalimide in acetone at reflux failed, the use of DMF as solvent at 90°C led to compound **3**. The required amine **5** was obtained by the Ing-Manske[13] procedure. This first novel method proceeds in 50% overall yield from **1**.

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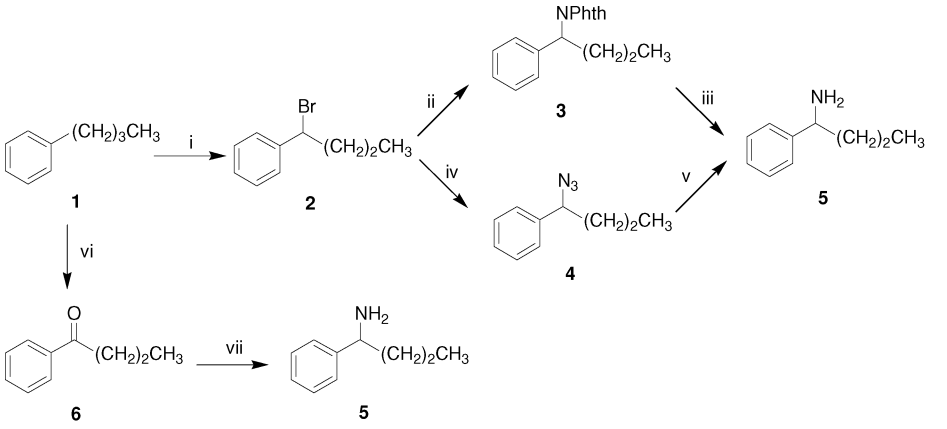

(i) NBS, CCl_4, 80°C, 3h (ii) KPhth/DMF, 90°C (iii) $NH_2NH_2.H_2O$, MeOH, 80°C (iv) NaN_3 (v) PPh_3, KOH, 18% HCl (vi) TBHP, CrO_3, EDC (vii) $HCOONH_4$, conc.HCl

Scheme

The second method involves the transformation of **2** to α-azidophenylbutane (**4**), using sodium azide. Reaction of **4** with triphenylphosphine in ether at RT for 3 h gave the corresponding iminophosphorane, which was hydrolyzed with aqueous alkali to afford the required amine **5**. The ^{1}H NMR data of (**5**) from both reactions was in complete agreement with its structure. The overall yield of compound (**5**) is 46% starting from **1**.

The third route involved the conversion of *n*-butylbenzene to 1-phenyl-1-butanone (**6**) followed by the Leuckart reaction conditions. In 1987, Muzart[14] reported chromium catalyzed benzylic oxidations using *t*-butyl hydroperoxide (TBHP).[15] Accordingly a process for the preparation of 1-phenyl-1-butanone (**6**) from *n*-butylbenzene *via* benzylic oxidation using catalytic CrO_3 in combination with TBHP under homogenous conditions on 150 g batch size was developed. Treatment of (**6**) with ammonium formate led to the corresponding formamide, which, without isolation, was hydrolyzed, with conc. HCl to give the desired amine **5** in 50% yield. The reductive amination of **6** has been performed on 100 g scale and yields were optimized. However, the overall yield of **5** is only 31% starting from compound **1**. Of the three methods, the first method was found to be superior in terms of overall yield and convenience.

Experimental Section

Melting points were measured with a Fischer-Johns melting point apparatus, and are not corrected. The ^{1}H NMR spectra were recorded at GEMINI 200 MHz, BRUKER Avance 300 MHz and UNITY 400 MHz spectrometers with tetramethylsilane as an internal reference. Mass spectra (MS) were measured on 7070 H (Manchester, UK) mass spectrometers using a direct inlet probe. IR spectra were obtained on Thermo Nicolet Nexus 670 FT-IR spectrometer. For column chromatography, silica gel 60–120 mesh was used. For TLC, silica gel $60F_{254}$ (Merck) was used.

α-Bromophenylbutane (2)

o a stirred solution of *n*-butylbenzene (**1**, 3.5 g, 26.1 mmol) in CCl_4 (18 mL) was added NBS (5.55 g) at r.t. The mixture was refluxed for 3 h and then was cooled to 0°C. The precipitated succinimide was filtered off and the filtrate was evaporated *in vacuo* to give the title compound **2** (4.98 g, 90%) as a brown colored liquid. The crude compound **2**, bp. 67–72°C/1mm (*lit.*[16] bp. 67–75°C/1mm), was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1. 0 (t, 3H, CH_3), 2.2 (m, 2H, CH_2), 2.6 (q, 2H, CH_2), 5.0 (t, 1H, CH), 7.4–7.6 (m, 5H, ArH).

Anal. Calcd. for $C_{10}H_{13}Br$: C, 56.36; H, 6.15. Found: C, 56.22; H, 6.13.

α-Phthalimidophenylbutane (3)

To a stirred solution of potassium phthalimide (3.14 g, 16.97 mmol) in DMF (10 mL) was added dropwise α-bromophenylbutane (**2**), 3.0 g, 14.15 mmol). The mixture was heated at 90°C for 3.5 h. After completion of the reaction, the reaction mixture was poured into water (25 mL) and extracted into ether (2 × 15 mL). The organic phase was separated, dried and evaporated in *vacuo* to afford the crude product which was purified by column chromatography on silica gel using hexane: ethylacetate (7:3) to give the title compound (**3**) (4.01g, 82%) as a semi-solid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1. 0 (t, 3H, CH_3), 1.4 (m, 2H, CH_2), 2.2, 2.4 (2 × q, 2H, CH_2), 5.3 (t, 1H, CH), 7.1–7.7 (m, 9H, ArH); MS: *m/z* = 279 [M+, 20].

Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13. Found : C, 77.12; H, 6.10.

1-Amino-1-phenylbutane (5)

To a stirred solution of α-phthalimidophenylbutane (**3**, 12.0 g, 43 mmol) in MeOH (60 mL) was added hydrazine hydrate (3.2 g, 64.5 mmol). The mixture was refluxed for 2.5 h and the solvent was evaporated in *vacuo* and to the liquid residue hexane (2 × 25 mL) was added at 0°C. The separated solid was filtered off and the filtrate evaporated under reduced pressure to give title compound **5** (4.35 g, 69%) as a colorless liquid, bp. 63°C/10mm (*lit.*[6] bp. 102°C/14mm), mp. 248–250°C (dec) [*lit.*[7] mp. 250°C (dec)] (hydrochloride). IR (KBr): 3370, 3310 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.9 (t, 3H, CH_3), 1.2 (m, 2H, CH_2), 1.6 (q, 2H, CH_2), 3.9 (t, 1H, CH), 7.2 (m, 5H, ArH); MS: *m/z* = 149 [M+, 100].

Anal. Calcd. for $C_{10}H_{15}N$: C, 80.48; H, 10.13. Found: C, 80.23; H, 9.93.

α-Azidophenylbutane (4)

To a stirred solution of NaN_3 (22.0 g, 0.34 mol) in water (50 mL) and MeOH (200 mL) was added α-bromophenylbutane (**2**, 20.0 g, 0.09 mol). The solution was stirred at r.t for 8 h, then methanol was evaporated in *vacuo* and the aqueous layer extracted into dichloromethane (2 × 50 mL). The organic phase was separated, dried and concentrated to afford the crude product, bp. 85–90°C/4mm (lit.[16] bp. 81–87°C/3mm), which was distilled to give the pure title compound **4** (13.18 g, 80%) as a colorless liquid. IR (KBr): 2097 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.9 (t, 3H, CH_3), 1.2–1.4 (m, 2H, CH_2), 1.6–1.7 (m, 2H, CH_2), 4.4 (t, 1H, CH), 7.2–7.4 (m, 5H, ArH).

Anal. Calcd. for $C_{10}H_{13}N_3$: C, 68.54; H, 7.48. Found : C, 68.42; H, 7.33.

1-Amino-1-phenylbutane (5) from α-Azidophenylbutane

To a stirred solution of α-azidophenylbutane (**4**, 1.0 g, 5.7 mmol) in diethyl ether (10 mL) was added dropwise a solution of Ph_3P (1.5 g, 5.7 mmol) in diethyl ether (20 mL). The contents were stirred at r.t. for 3 h and the solvent was evaporated in *vacuo* to afford the crude iminophosphorane to which was added boiling EtOH (20 mL) and 2M aq. KOH (20 mL). The reaction mixture was stirred at r.t for 1 h, and then was made acidic by addition of 18% aq. HCl (40 mL) followed by reflux for 2 h. The solvent was evaporated and the aqueous layer was extracted into ethyl acetate (2 × 10 mL). The aqueous phase was separated and made alkaline with aq. NaOH, then extracted into dichloromethane (2 × 15 mL). The separated organic phase was dried and concentrated to afford the title compound **4** (0.54 g, 63%) as a colorless liquid, identical to the previously prepared compound.

1-Phenyl-1-butanone (6)

To a stirred solution of ethylene dichloride (200 mL) and CrO_3 (5 g, 0.05 mol) was slowly added a first portion of TBHP (190 mL) at 10–20°C (addition time 30 min). Then a solution of *n*-butylbenzene (**1**, 150 g, 1.2 mol) in ethylene dichloride (100 mL) was added. The mixture was heated to an internal temperature of 70–75°C for 2 h. Then a second portion of TBHP (190 mL) was slowly added (30 min) under reflux conditions. Similarly after every 1.5 h, third and fourth portions of TBHP (2 × 190 mL) were added, and reflux was continued for additional 12 h. Then a solution of $FeSO_4$ (1 g) in 250 mL of water was added, the mixture was stirred for 15 min and allowed to separate into an upper organic and a lower aqueous phase. The organic phase was washed with aqueous ammonia solution (120 mL ammonium hydroxide in 300 mL water). The separated lower aqueous ammonia phase was neutralized with 50% aq. HCl (135 mL) to give a filterable solid which was identified as benzoic acid.

The organic phase was dried, concentrated and fractionated under *vacuum* (20 mm) to afford 3 fractions. The first fraction (34 g) at 90°C consisted of unreacted **1**, the second fraction (20 g) at 95–120°C consisted of a mixture of *n*-butylbenzene and product **6** in the ratio of 2:3. The third fraction at 120–135°C contained pure compound **6** (79.5 g, 62% based on the recovery of butylbenzene) as a yellowish liquid, bp. 100–102°C/10mm (*lit*.[17] bp. 110°C/10mm); IR (KBr): 1698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.0 (t, 3H, CH_3), 1.7 (m, 2H, CH_2), 3.0 (t, 2H, CH_2), 7.4–7.5 (m, 5H, ArH); MS: *m/z* = 148 [M+, 100].

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found : C, 81.12; H, 8.18.

1-Amino-1-phenylbutane (5) from 1-Phenyl-1-butanone (6)

A mixture of 1-phenyl-1-butanone (**6**, 100 g, 0.67 mol) and ammonium formate (136 g, 0.46 mol) was heated. At 120°C, the reaction mixture became homogenous and at 150°C 1-phenyl-1-butanone and water distilled out. The organic phase was separated, poured back into the reaction flask and the mixture maintained at 180°C for 6 h. After completion of the reaction, the mixture was poured into water (500 mL) and extracted into benzene (600 mL). The organic phase was separated, dried and concentrated to give the crude formamide (110 g). Conc. HCl (97 g) was added to the crude formamide and the reaction was heated at 110°C for 2 h. Then the mixture was poured into water (400 mL) and washed

with benzene (2 × 250 mL). The aqueous phase was separated and made alkaline with aq. NaOH, extracted into DCM (2 × 100 mL). The separated organic phase was dried and concentrated to afford the crude product, which was distilled under vacuum to afford the title compound **5** (53 g, 50%) as a colorless liquid, bp. 63°C/10mm, identical to the previously prepared compound.

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