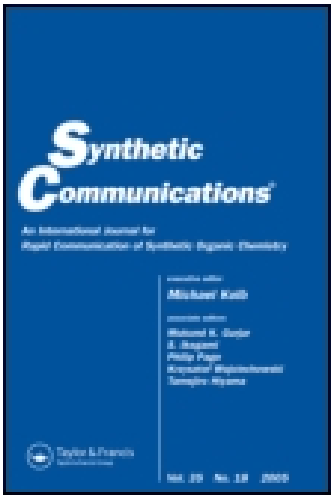

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Efficient Routes Toward 4-[(2-Aminoethoxy)methyl]benzophenone

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Efficient Routes Toward 4-[(2-Aminoethoxy)methyl]benzophenone

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Abstract: The novel benzophenone derivative 4-[(2-aminoethoxy)methyl]benzophenone (**4**) was synthesized via two pathways, commencing from 4-(bromomethyl)-benzophenone (**1**) and methyl 4-(bromomethyl)benzoate (**7**) respectively. All new compounds were characterized by ^{1}H NMR, MS, IR, and EA.

Keywords: 4-[(2-Aminoethoxy)methyl]benzophenone, photophobes, synthesis

Recently, benzophenone photoprobes[1,2] have been extensively used to study nucleotide, receptor, and enzyme binding sites; equipped with chemically reactive groups, the benzophenone-containing reagents have also been employed as cross-linkers to investigate intramolecular as well as protein–protein interactions.[3–5] The benzophenone photoprobes are superior to other photoactivatable groups in that the benzophenone group is chemically more stable and can be photoactivated at 350–360 nm, avoiding protein-damaging in shorter wavelengths. With the aim of developing new and more efficient benzophenone photoprobes, we designed three routes toward a novel benzophenone derivative, 4-[(2-aminoethoxy)methyl]benzophenone (**4**), as shown in Schemes 1–3.

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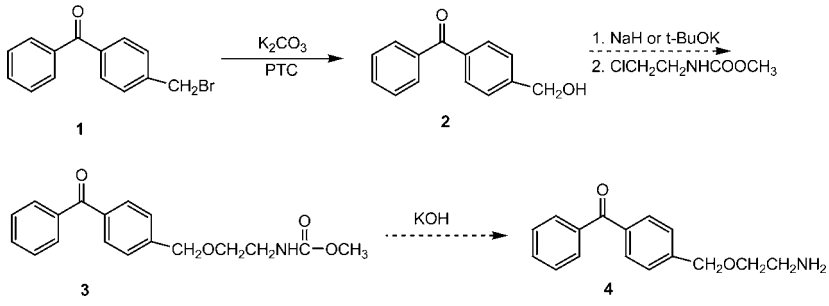
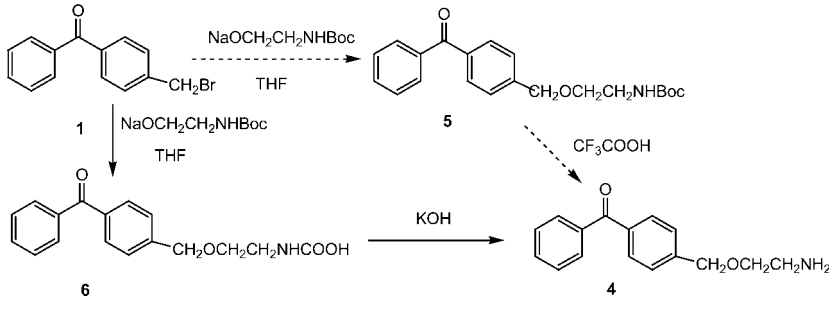


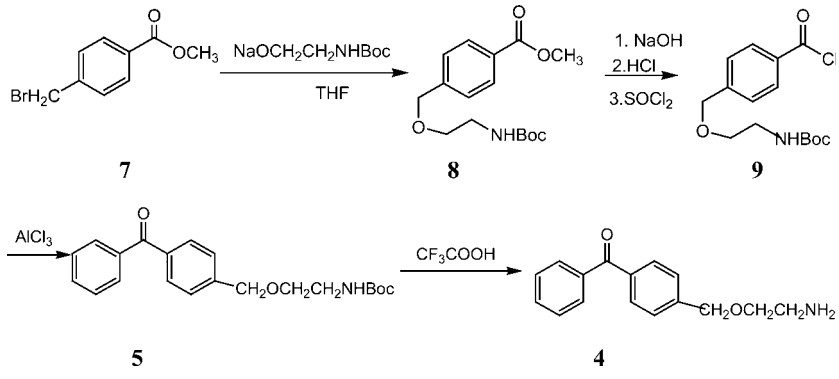
Scheme 1.

To date, there have been no reported syntheses of compounds **6**, **8**, and **9**. Oatis et al.[2] have reported the synthesis of 4-(hydroxymethyl)benzophenone (**2**) by hydrolysis of **1** with potassium carbonate in refluxing in water for 48 h. We improved upon this reaction by employing benzyltriethylammonium chloride as a phase-transfer catalyst and stirring the reaction for 5 h at room temperature to give **2** in 77% yield (Scheme 1). The benzyl alcohol **2** was successfully converted to its metal salt by treatment with either sodium hydride or *t*-BuOK and was subsequently exposed to methyl (2-chloroethyl)carbamate ($ClCH_2CH_2NHCOOCH_3$) under standard Williamson conditions in different solvents (THF, dioxane). Surprisingly, the expected etherification reaction failed to take place; no trace of the desired product **3** was detected by GC-MS and the major compound isolated by purification was unreacted **2**. This revealed that the chloride leaving group of the carbamate is not reactive enough to be displaced by the anion of **2**. It was expected that the target **4** could be formed from **3** by base-mediated removal of the acetyl group.

Yibo Zhou et al.[6] have reported the synthesis of aminoethoxy-containing compounds from chlor-pyridazinones and salts of ethanolamine (e.g., $NaOCH_2CH_2NH_2$). Based on this literature precedent, we envisaged that **4** could be prepared by treatment of **1** with $NaOCH_2CH_2NH_2$. Experimentally,



Scheme 2.



Scheme 3.

this resulted in the formation of many by-products, including the Schiff base obtained by reaction of the carbonyl group of **1** with the amino group of ethanolamine. Fortunately, after the amino functionality was protected[7] as the *t*-butoxycarbonyl (Boc) group with Boc anhydride, the ether **4** could be conveniently prepared in high yield by treatment of bromide **1** with $NaOCH_2CH_2NHBoc$, followed by basic hydrolysis (Scheme 2). Our original intention was to convert **1** to **4** via Boc-protected **5**, but unexpectedly the acid **6** formed by partial hydrolysis, rather than **5**, was obtained as the intermediate. Treatment of **6** with base completed the very facile synthesis of **4**.

Another route for the synthesis of **4** was investigated, commencing from methyl 4-(bromomethyl)benzoate **7**. This was initially treated with $NaOCH_2CH_2NHBoc$ in THF to yield **8**. After the ester **8** was converted to the acid chloride **9** in three high-yielding steps, a classical Friedel–Crafts reaction was employed to prepare the Boc-protected amine **5**. Benzene was treated with **9** and catalytic aluminium trichloride, yielding **4** after acidic hydrolysis of the Boc group of **5**.

In summary, we have presented two facile routes for the preparation of 4-[(2-aminoethoxy)methyl]benzophenone (**4**), commencing from either 4-(bromomethyl)benzophenone (**1**) or methyl 4-(bromomethyl)benzoate (**7**), and Boc-protected ethanolamine.

EXPERIMENTAL

General

All reactions were monitored by TLC on silica-gel F-254 plates (Merck) with detection under UV light. Uncorrected melting points were determined using a XRC-1 apparatus. All ^1H NMR spectra were recorded at 297 K on a 400 MHz apparatus as samples in $CDCl_3$. Chemical shifts are reported as

δ (ppm) relative to $CHCl_3$, fixed at 7.26 ppm for ^1H NMR. Infrared spectra were measured on a Perkin-Elmer 1600 FTIR spectrophotometer as KBr pellets. GC-MS data were measured with a HP 5988 instrument.

Compound **1** was synthesized by the method of Houlihan and Nadelson.[8]

4-(Hydroxymethyl)benzophenone (2)

A mixture of **1** (11.0 g, 40 mmol), K_2CO_3 (15.2 g, 120 mmol), and benzyltriethylammonium chloride (1.0 g) in water (100 mL) was stirred at room temperature for 8 h. The product was extracted into ethyl acetate (2×100 mL), and the organic extracts were dried over Na_2SO_4. The solvent was removed by evaporation to give a yellow solid (7.8 g), which was crystallized from propanol to give **3** (6.5 g, 77.0%), mp 98–100°C (lit.[2] 59–61°C). ^1H NMR: δ 7.77–7.61 (m, 5H, Ar-H), 7.50–7.46 (dd, 4H, $J = 7.6$ Hz), 4.79 (s, 2H, CH_2). MS (m/e): 212 (M^+), 135, 105.

4-([(2-Carboxyamino)ethoxy]methyl)benzophenone (6)

t-Butoxycarbonyl anhydride (7.3 g, 32 mmol) was dropwise added to a solution of ethanolamine (2.0 g, 32 mmol) in THF (20 mL) with the temperature kept below 0°C using an ice–salt bath. After the addition was complete, the reaction mixture was stirred at room temperature for about 30 min. The reaction mixture was concentrated, and the crude product was diluted with ethyl acetate, washed with water, and dried over Na_2SO_4. Evaporation of the solvent yielded crude $HOCH_2CH_2NHBoc$ as an oily residue (5.2 g). Na (0.23 g, 10 mmol) was added to a solution of $HOCH_2CH_2NHBoc$ (1.61 g, 10 mmol) in anhydrous THF (20 mL) and the reaction mixture was stirred until no Na remained. Having generated $NaOCH_2CH_2NHBoc$ in situ, a solution of **1** (2.5 g, 9 mmol) in THF (10 mL) was added, and the reaction was refluxed for about 5 h. The mixture was cooled, the solvent was evaporated, and the residue was diluted with ethyl acetate (20 mL). HCl (3 N) was added dropwise until pH 5 was reached, and the aqueous phase was extracted with ethyl acetate (2×10 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (20 mL), and water (20 mL) and dried over Na_2SO_4. After the solvent was evaporated, the crude product was purified by crystallization from ethanol to give **6** (2.3 g, 87%), mp 63–64°C. ^1H NMR: δ 7.81–7.79 (dd, 4H, $J = 7.5$ Hz, Ar–H), 7.62–7.58 (t, 1H, $J = 7.2$ Hz, Ar–H), 7.51–7.50 (t, 2H, $J = 7.8$ Hz, Ar–H), 7.42–7.40 (d, 2H, $J = 8.0$ Hz, Ar–H), 4.52 (s, 2H, Ar–CH_2), 4.35 (t, 2H, $J = 8.0$ Hz, –OCH_2), 3.48 (t, 2H, $J = 8.0$ Hz, –CH_2–). MS (m/e): 281 ($M^+ - H_2O$), 255, 204, 176, 105. IR (KBr): 3447, 2985, 2898, 1734, 1651, 1596, 1575, 1521 cm^{-1}. Elemental analysis calcd. for $C_{17}H_{17}NO_4$: C, 68.23; H, 5.69; N, 4.68. Found: C, 68.71; H, 5.62; N, 4.66.

4-[(2-Aminoethoxy)methyl]benzophenone (4) from Acid 6

To a solution of **6** (1 g, 3.3 mmol) in 95% ethanol (10 mL) was added 30% NaOH (10 mmol). After stirring for 5 h at room temperature, the reaction mixture was concentrated and the crude product was obtained as a yellow oil. Purification by flash chromatography gave **4** (0.81 g, 97%) as a yellow oil. ^{1}H NMR: δ 7.80–7.77 (m, 4H, Ar–H), 7.61–7.57 (m, 1H, Ar–H), 7.50–7.43 (m, 4H, Ar–H), 3.90 (s, 2H, $ArCH_2$), 3.71–3.68 (t, 2H, OCH_2), 2.84–2.82 (t, 2H, CH_2N), 2.22 (s, 2H, NH_2); MS (m/e): 254 ($M^+ - 1$), 224, 195, 167, 105. IR (KBr): 3304, 2950, 2837, 1654, 1606, 1557, 1176, 1051, 841, 701 cm^{-1}. Elemental analysis calcd. for $C_{16}H_{17}NO_2$: C, 75.29; H, 6.67; N, 5.49. Found: C, 75.71; H, 6.52; N, 5.46.

Methyl 4-[(2-[(*t*-butoxycarbonyl)amino]ethoxy)methyl]benzoate (8)

Na (2.3 g, 100 mmol) was added to a solution of $HOCH_2CH_2NHBoc$ (16.1 g, 100 mmol) in THF (150 mL), and the reaction was stirred for 8 h until no Na remained. Compound **7** (19.1 g, 90 mmol) was added to this solution of the sodium salt in anhydrous THF (100 mL), and the reaction was refluxed for about 5 h. The reaction mixture was concentrated, and the residue was diluted with $CHCl_3$ (100 mL). HCl (5%) was added dropwise until pH 5 was reached, and the aqueous phase was extracted with $CHCl_3$ (2×30 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (80 mL) and water (80 mL) and dried over Na_2SO_4. After the solvent was evaporated, the crude product was purified by crystallization from ethyl acetate to give **6** (24.5 g, 87%), mp 56–58°C. ^{1}H NMR: δ 8.00 (s, 1H, NH), 7.89 (d, 2H, $J = 7.4$ Hz, Ar-H), 7.31 (d, 2H, $J = 7.5$ Hz, Ar–H), 4.68 (s, 2H, Ar–CH_2), 4.13 (t, 2H, $J = 7.8$ Hz, –OCH_2), 4.01 (s, 3H, OCH_3), 3.87 (t, 2H, $J = 8.0$ Hz, –CH_2N–), 1.40 (s, 9H, –$C(CH_3)_3$). MS (m/e): 294 (M^+–CH_3), 252(M–C_4H_9). Elemental analysis calcd. for $C_{16}H_{23}NO_5$: C, 62.14; H, 7.44; N, 4.53. Found: C, 62.58; H, 7.52; N, 4.59.

4-[(2-[(*t*-Butoxycarbonyl)amino]ethoxy)methyl]benzoyl Chloride (9)

To a solution of **8** (11.7 g, 40 mmol) in methanol (100 mL) was added 30% NaOH (30 mL), and the reaction was stirred at room temperature for 24 h. The reaction mixture was concentrated and acidified to pH 5 with 5% HCl. The product was extracted into ethyl acetate (3×50 mL), and the combined organic extracts were washed with saturated NaCl solution (80 mL) and dried over Na_2SO_4. After the solvent was evaporated, $SOCl_2$ (25 mL, 343 mmol) was added to the residue, and the reaction was heated at reflux under N_2 for 4 h. The excess $SOCl_2$ was removed under reduced pressure, and the crude solid obtained was purified by crystallization from

benzene to give **9** (9.9 g, 79%), mp 52–54°C. ^{1}H NMR: δ 8.05 (s, 1H, NH), 7.98 (d, 2H, $J = 7.2$ Hz, Ar–H), 7.31 (d, 2H, $J = 7.1$ Hz, Ar–H), 4.57 (s, 2H, Ar–CH_2), 4.09 (t, 2H, $J = 7.8$ Hz, –OCH_2), 3.84 (t, 2H, $J = 8.0$ Hz, –CH_2N–), 1.36 [s, 9H, –$C(CH_3)_3$]. MS (m/e): 313(M^+), 315 ($M^+ + 2$), 283 ($M^+ - 2CH_3$), 256 ($M - C_4H_9$). Elemental analysis calculated for $C_{15}H_{20}ClNO_4$: C, 57.42; H, 6.38; N, 4.47. Found: C, 56.95; H, 6.35; N, 4.46.

4-[(2-[(*t*-Butoxycarbonyl)amino]ethoxy)methyl]benzophenone (5)

A solution of **9** (2.5 g, 9 mmol) in THF (20 mL) was dropwise added to a suspension of anhydrous $AlCl_3$ (2.7 g, 20 mmol) in benzene (50 mL) and the mixture was refluxed for 2 h. The reaction was cooled to room temperature and poured into a mixture of 36% HCl (10 mL) and ice. The aqueous layer was extracted with benzene (2 × 10 mL), and the organic extracts were washed with saturated $NaHCO_3$ solution (20 mL) and water (20 mL) and dried over Na_2SO_4. After the solvent was evaporated, the crude product was purified by crystallization from ethanol to give **5** (2.6 g, 81%), mp 47–49°C. ^{1}H NMR: δ 7.86–7.81 (dd, 4H, $J = 7.2$ Hz, Ar-H), 7.63–7.40 (m, 5H, Ar–H), 4.58 (s, 2H, Ar–CH_2), 4.45 (t, 2H, $J = 8.0$ Hz, –OCH_2), 3.38 (t, 2H, $J = 8.0$ Hz, –CH_2–), 1.48 [s, 9H, –$C(CH_3)_3$]. MS (m/e): 325 ($M^+ - 2CH_3$), 298 ($M - C_4H_9$), 254, 224, 195. Elemental analysis calcd. for $C_{21}H_{25}NO_4$: C, 70.99; H, 7.04; N, 3.94. Found: C, 71.32; H, 7.22; N, 4.01.

4-[(2-Aminoethoxy)methyl]benzophenone (4) from Boc Derivative 5

The Boc group of **5** was removed with CF_3COOH (1.1 eq) in CH_2Cl_2 via the method of Ref. 9, giving **4** (yield, 97%).

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