Benzhydrylamine: an effective aminating agent for the synthesis of primary amines

Quan-Wei Sun, Jun-De Xing*, Yu-Hong Qin, Xu-Wen Yin and Yi Zhou

College of Chemistry and Chemical Engineering, Taiyuan University of Technology, Taiyuan 030024, P.R. China

Aldehydes, ketones, alkyl toluene-*p*-sulfonates and halides are converted into the corresponding primary amines with benzhydrylamine as a valuable ammonia synthon in moderate to excellent yields.

Keywords: benzhydrylamine, synthesis of primary amines, hydrolysis

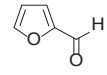
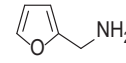
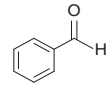
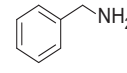
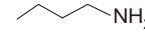
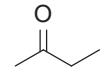
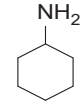
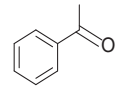
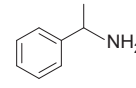
Many primary amines are biologically active compounds or form their synthetic building blocks. Important methods for the synthesis of primary amines include the alkylation of ammonia by organic halides and alcohols,[1–3] the reductive amination of carbonyl compounds,[4,5] the reduction of nitro compounds[6,7] and nitriles,[8,9] as well as other methods.[10–12] The synthesis of primary amines has been reported[13,14] from benzylamine and carbonyl compounds *via* the [1,3]-prototropic isomerisation of an imine followed by a hydrolysis step. This is a useful procedure for the preparation of primary amines avoiding the formation of secondary and tertiary amines as byproducts. However, benzylamine has a moderate reactivity as an aminating agent in organic synthesis and its application is limited. Triphenylmethylamine as an alternative reagent has been applied for the conversion of alkyl halides and alkyl tosylates to the corresponding primary amines but is restricted by its high cost.[15] Consequently, it is still a challenge to develop new aminating agents for a facile and effective synthetic method of primary amines.

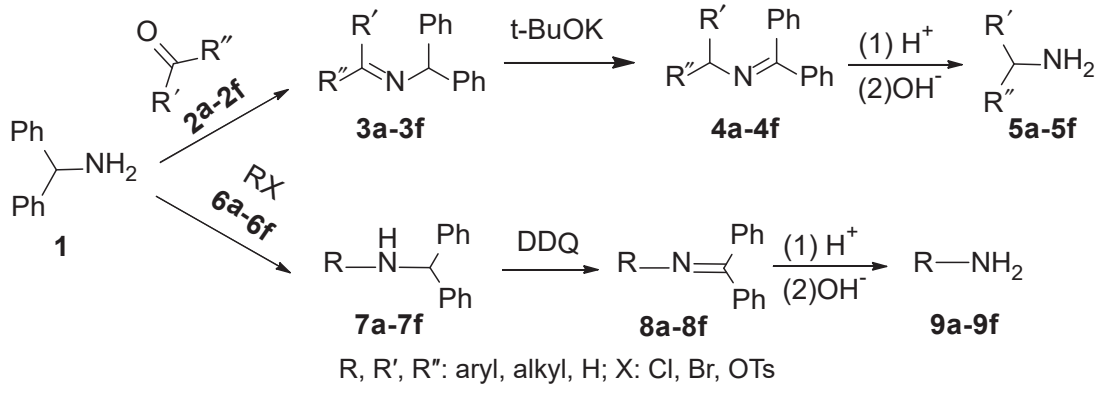
We report a high-yielding, low-cost synthesis of primary amines by the amination of aldehydes, ketones, and alkyl toluene-*p*-sulfonates and halides using benzhydrylamine as an ammonia synthon (Scheme 1).

Results and discussion

The primary amines that were prepared from aldehydes and ketones using benzhydrylamine as an aminating agent are shown in Table 1. Furfural, benzaldehyde and *n*-butyraldehyde reacted with benzhydrylamine in dichloromethane as a solvent to afford **3a**–**c**. However, benzhydrylamine did not react with butanone, cyclohexanone and 1-phenylethanone in CH_2Cl_2. The reactivity of aldehydes is higher than that of ketones as the steric hindrance of an aldehyde group is less than that of a ketone group. Butanone or cyclohexanone were used as both the starting material and the solvent in the reaction with benzhydrylamine to obtain **3d** and **3e**. Acetophenone with toluene as the solvent reacted with benzhydrylamine to obtain **3f**. Then with DMSO as the solvent and potassium *tert*-butoxide as the catalyst, **4a**–**f** were obtained by isomerisation of the double bond of **3a**–**f**. Ethanolamine, tetrabutylammonium bromide, sodium methylate, sodium acetate and sodium bydride were used as catalysts to replace potassium *tert*-butoxide in this experiment, but the results were not as good as those with

Table 1 Synthesis of primary amines **5a–f** from aldehydes and ketones

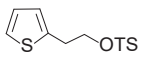
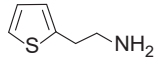
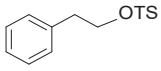
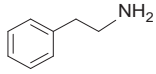
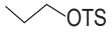
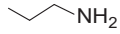
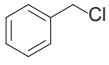
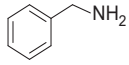
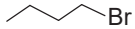
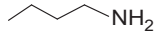
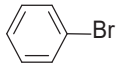
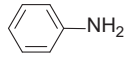
Aldehydes and ketones	Primary amines	Yield (%)
 **2a**	 **5a**	86
 **2b**	 **5b**	81
 **2c**	 **5c**	69
 **2d**	 **5d**	64
 **2e**	 **5e**	67
 **2f**	 **5f**	72



Scheme 1 General scheme for preparation of a primary amine.

* Correspondent. E-mail: xingjunde@126.com

Table 2 Synthesis of primary amines **9a–f** from alkyl toluene-*p*-sulfonates and halides

RX	Primary amines	Yield (%)
		91
6a	**9a**	
		93
6b	**9b**	
		88
6c	**9c**	
		85
6d	**9d**	
		79
6e	**9e**	
		72
6f	**9f**	

potassium *tert*-butoxide. The amines were **5a–f** obtained by acid hydrolysis of **4a–f**.

Primary amines were synthesised by treating alkyl toluene-*p*-sulfonates or halides with benzhydrylamine. The reactants and the products are shown in Table 2. Compounds **7a–f** were obtained by the reaction of **6a–f** with benzhydrylamine dissolved in acetonitrile, using sodium carbonate to neutralise the acid. The reaction of the bromo compounds with benzhydrylamine was slow. Although there are many ways to break a C–N bond in secondary amines, these particular bonds were difficult to cleave. We used the literature methods[16–18] with **7a–f**, expecting to obtain **9a–f**, but the yields were almost zero. However, compared with a C–N single bond, a C=N double bond can be easily broken. Compounds **8a–f** were easily obtained by the reaction of **7a–f** with DDQ. Finally, the corresponding primary amines **9a–f** were obtained by the hydrolysis of the C=N bond in sulfuric acid (1.4 mol L^{-1}).

In conclusion, we have shown that benzhydrylamine can be used to convert aldehydes, ketones, and alkyl toluene-*p*-sulfonates and halides to amines. Aryl aldehydes and ketones gave higher yields than their alkyl counterparts with the aldehydes giving better yields than the ketones. Dehydrogenation of the secondary amine obtained from the reaction of benzhydrylamine and an alkyl toluene-*p*-sulfonate or halide to an imine provided a route to a primary amine that was not contaminated by secondary or tertiary amine byproducts. Benzhydrylamine was more reactive than benzylamine in this context and is cheaper than tritylamine.

Experimental

Chemicals of high purity were purchased from Sinopharm Chemical Reagent Co. Ltd. and used without further purification. The reactions were monitored by TLC, and all yields refer to isolated products. ^{1}H NMR spectra were obtained on a Bruker 400 MHz spectrometer or a Bruker 600 MHz spectrometer in $CDCl_3$ or DMSO-d_6 using tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are given in ppm and coupling constants (*J*) are in Hertz (Hz). Melting points were obtained using an Electrothermal YRT-3 apparatus. Infrared spectra were recorded on a Shimadzu FTIR-8400S spectrometer in KBr with absorption values given in cm^{-1}.

Synthesis of benzhydrylamine[19] (**1**)

A mixture of benzophenone (1.37 mol), formamide (250 mL) and formic acid (85%, 31.50 mL) was heated to 190 °C for 3 h. The reaction mixture was cooled to 140 °C and poured into cold water (1.20 L). The resulting precipitate was collected by filtration, to which concentrated aqueous hydrochloric acid (230 mL) was added, and the reaction mixture was heated under reflux with vigorous stirring. The hydrochloride salt was collected by filtration and washed with diethyl ether. The white crystals were treated with an aqueous solution of sodium hydroxide (2.80 M) and extracted with diethyl ether. The organic layer was distilled under reduced pressure to afford benzhydrylamine **1** as a white solid; yield 94%; m.p. 293–294 °C (lit.[20] 294–296 °C); FTIR (KBr) (ν_{max} cm^{-1}): 2956, 2852 (NH_3^+); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.34 (s, 3H), 7.60–7.58 (m, 4H), 7.42–7.38 (m, 4H), 7.35–7.31 (m, 2H), 5.61 (s, 1H).

Synthesis of **5a** *and* **5b***; general procedure*

The arylaldehyde **2a** or **2b** (0.50 mol) was added to a solution of benzhydrylamine (0.50 mol) in CH_2Cl_2 (230 mL) at room temperature. After completion of the reaction, (TLC), the solvent was removed under reduced pressure. The residue was dissolved in DMSO (850 mL) and heated to 40 °C and portions of potassium *tert*-butoxide (0.13 mol) were added over 10 min with stirring. After 10 min, the reaction mixture was heated to 55 °C for about 12 h, evaporated *in vacuo* and treated with H_2SO_4 (1.40 M, 885 mL) at room temperature. After completion of the hydrolysis (TLC), the aqueous phase was extracted with CH_2Cl_2, and separated into organic and aqueous layers. The aqueous phase was adjusted to a basic pH by sodium hydroxide solution (40%), extracted with CH_2Cl_2 and then the organic phase was distilled under reduced pressure to yield the expected products **5a** and **5b**.

2-Furanmethanamine (**5a**): Colourless liquid; yield 86%; FTIR (KBr) (ν_{max} cm^{-1}): 3365, 3274 (N–H); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.49 (s, 1H), 7.18 (d, *J* = 3.4 Hz, 1H), 6.54 (t, *J* = 1.8 Hz, 1H), 6.30 (s, 1H), 5.87 (s, 1H), 3.01 (s, 2H).

Benzylamine (**5b**) *hydrochloride*: White solid; yield 81%; m.p. 262–263 °C (lit.[21] 264–265 °C); FTIR (KBr) (ν_{max} cm^{-1}): 3004, 2969 (NH_3^+); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (s, 3H), 7.54–7.52 (m, 2H), 7.42–7.34 (m, 3H), 3.99 (s, 2H).

Synthesis of 1-butanamine (**5c**)

n-Butyraldehyde **2c** (0.50 mol) was added to a mixture of benzhydrylamine (0.50 mol) and Na_2SO_4 (0.25 mol) in CH_2Cl_2 (230 mL) at room temperature. The flask was then heated to reflux. After completion of the reaction (TLC), the mixture was cooled, filtered and evaporated *in vacuo*. The residue was dissolved in DMSO (850 mL) and heated to 40 °C. Portions of potassium *tert*-butoxide (0.13 mol) were added over 10 min with stirring. After 10 min, the reaction mixture was heated to 55 °C for about 12 h, evaporated *in vacuo* and treated with H_2SO_4 (1.40 M, 885 mL) at room temperature. After completion of the hydrolysis (TLC), the aqueous phase was extracted with CH_2Cl_2, followed by separation of the organic and aqueous layers. The aqueous phase was adjusted to a basic pH by sodium hydroxide solution (40%), extracted with CH_2Cl_2 and then the organic phase distilled under reduced pressure to yield 1-butanamine **5c** as: Colourless liquid; yield 69%; FTIR (ν_{max} cm^{-1}): 3357, 3300 (N–H); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.54 (t, *J* = 6.9 Hz, 2H), 1.30–1.15 (m, 6H), 0.77 (t, *J* = 7.2 Hz, 3H).

Synthesis of **5d** *and* **5e**; *exemplified by 2-butanamine* (**5d**)*; general procedure*

A mixture of benzhydrylamine (0.50 mol), butanone **2d** (3.33 mol) and Na_2SO_4 (0.25 mol) was heated at 70 °C. After completion of the reaction (TLC), the mixture was cooled, filtered and evaporated *in vacuo*. The residue was dissolved in DMSO (850 mL), heated to 40 °C and portions of potassium *tert*-butoxide (0.13 mol) were added over 10 min with stirring. After 10 min, the reaction mixture was heated to 55 °C for about 12 h, evaporated *in vacuo* and treated with H_2SO_4 (1.40 M, 885 mL) at room temperature. After completion of the hydrolysis (TLC), the aqueous phase was extracted with CH_2Cl_2, followed by separation of the organic and aqueous layers. The aqueous phase was adjusted to a basic pH by sodium hydroxide solution (40%), extracted with CH_2Cl_2 and

then the organic phase was distilled under reduced pressure to yield the expected product **5d**.

2-Butanamine (**5d**): Colourless liquid; yield 64%; FTIR (KBr) (ν_{max} cm^{-1}): 3338, 3283 (N–H); ^1H NMR (400 MHz, $CDCl_3$): δ 2.69–2.61 (m, 1H), 1.24–1.16 (m, 2H), 1.13 (s, 2H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.76 (t, *J* = 7.4 Hz, 3H).

Cyclohexanamine (**5e**): Colourless liquid; yield 67%; FTIR (KBr) (ν_{max} cm^{-1}): 3351, 3277 (N–H); ^1H NMR (400 MHz, $CDCl_3$): δ 2.51–2.43 (m, 1H), 1.69–1.65 (m, 2H), 1.59–1.54 (m, 2H), 1.47–1.43 (m, 1H), 1.17–1.05 (m, 4H), 1.02–0.84 (m, 3H).

Synthesis of 1-phenylethylamine (**5f**)

A mixture of benzhydrylamine (0.50 mol), acetophenone **2f** (0.50 mol), toluene (460 mL) and Na_2SO_4 (0.25 mol) was heated at 90 °C. After completion of the reaction (TLC), the reaction mixture was cooled, filtered and evaporated *in vacuo*. The residue was dissolved in DMSO (850 mL) and heated to 40 °C. Portions of potassium *tert*-butoxide (0.13 mol) were added over 10 min with stirring. After 10 min, the reaction mixture was heated to 55 °C for about 12 h, and then evaporated *in vacuo* and treated with H_2SO_4 (1.40 M, 885 mL) at room temperature. After completion of the hydrolysis (TLC), the aqueous phase was extracted with CH_2Cl_2, followed by separation of the organic and aqueous layers. The aqueous phase was adjusted to a basic pH by sodium hydroxide solution (40%), extracted with CH_2Cl_2 and then the organic phase was distilled under reduced pressure to yield 1-phenylthylamine **5f** as a colourless liquid; yield 72%; FTIR (KBr) (ν_{max} cm^{-1}): 3365, 3282 (N–H); ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.31 (m, 4H), 7.27–7.22 (m, 1H), 4.12–4.07 (q, *J* = 6.6 Hz, 1H), 1.70 (s, 2H), 1.39 (d, *J* = 6.7 Hz, 3H).

Synthesis of **9a**–**9d***; exemplified by 2-thiopheneethanamine* (**9a**)*; general procedure*

A mixture of benzhydrylamine (0.50 mol), CH_3CN (838 mL), 2-(2-thienyl) ethyl toluene-*p*-sulfonate **6a** (0.50 mol) and Na_2CO_3 (0.91 mol) was heated to 70 °C. After completion of the reaction, the reaction mixture was cooled, filtered and evaporated *in vacuo*. The residue was dissolved in benzene (1.03 L) and stirred at room temperature for 10 min, under a stream of N_2, and then portions of DDQ (1.09 mol) were added over 10 min with stirring. The reaction mixture was heated under reflux for 5 h, evaporated *in vacuo* and treated with H_2SO_4 (1.40 M, 885 mL) at room temperature. After completion of the hydrolysis, the aqueous phase was extracted with CH_2Cl_2, followed by separation of organic and aqueous layers. The aqueous phase was adjusted to a basic pH by sodium hydroxide solution (40%), extracted with CH_2Cl_2 and then the organic phase was distilled under reduced pressure to yield the expected product **9a**.

2-Thiophenylethylamine (**9a**): Colourless liquid; yield 91%; FTIR (KBr) (ν_{max} cm^{-1}): 3369, 3285 (N–H); ^1H NMR (400 MHz, $CDCl_3$): δ 7.11 (m, 1H), 6.94–6.90 (m, 1H), 6.81 (s, 1H), 2.94 (m, 4H), 1.24 (s, 2H).

2-Phenylethylamine (**9b**): Colourless liquid; yield 93%; FTIR (KBr) (ν_{max} cm^{-1}): 3370, 3283 (N–H); ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (t, *J* = 7.4 Hz, 2H), 7.21 (t, *J* = 7.7 Hz, 3H), 2.97–2.93 (m, 2H), 2.74 (t, *J* = 6.7 Hz, 2H), 1.18 (s, 2H).

1-Propylamine (**9c**): Colourless liquid; yield 88%; FTIR (KBr) (ν_{max} cm^{-1}): 3352, 3290 (N–H); ^1H NMR (400 MHz, $CDCl_3$): δ 2.41–2.36 (m, 2H), 1.24–1.14 (m, 2H), 1.03 (s, 2H), 0.67–0.62 (m, 3H).

Benzylamine (**9d**) *hydrochloride*: White solid; yield 85%; m.p. 262–263 °C (lit.[21] 264–265 °C); FTIR (KBr) (ν_{max} cm^{-1}): 3004, 2969 (NH_3^+); ^1H NMR (400 MHz, DMSO-d_6): δ 8.70 (s, 3H), 7.54–7.52 (m, 2H), 7.42–7.34 (m, 3H), 3.99 (s, 2H).

Synthesis of 1-butylamine (**9e**)

A mixture of benzhydrylamine (0.50 mol), CH_3CN (838 mL), KI (0.56 mol), Na_2CO_3 (0.91 mol) and 1-bromobutane **6e** (0.50 mmol) was heated under reflux. After completion of the reaction (TLC), the reaction mixture was cooled, filtered and evaporated *in vacuo*. The residue was dissolved in benzene (1.03 L) and stirred at room temperature for 10 min, under a stream of N_2, and then portions of DDQ (1.09 mol) were added over 10 min with stirring. The reaction mixture was heated under reflux for 5 h, evaporated *in vacuo* and treated with H_2SO_4 (1.40 M, 885 mL) at room temperature. After completion of the hydrolysis, the aqueous phase was extracted with CH_2Cl_2, followed by separation of organic and aqueous layers. The aqueous phase was adjusted to a basic pH by sodium hydroxide solution (40%), extracted with CH_2Cl_2 and then organic phase was distilled under reduced pressure to yield 1-butylamine (**9e**) as a colourless liquid; yield 79%; FTIR (KBr) (ν_{max} cm^{-1}): 3357, 3300 (N–H); ^1H NMR (400 MHz, $CDCl_3$): δ 2.54 (t, *J* = 6.9 Hz, 2H), 1.30–1.15 (m, 6H), 0.77 (t, *J* = 7.2 Hz, 3H).

Synthesis of aniline (**9f**)

A mixture of benzhydrylamine (0.50 mol), CH_3CN (838 mL), CuO (0.16 mol), Na_2CO_3 (0.91 mmol) and bromobenzene **6f** (0.50 mol) was heated under reflux. After completion of the reaction (TLC), the reaction mixture was cooled, filtered and evaporated *in vacuo*. The residue was dissolved in benzene (1.03 L) and stirred at room temperature for 10 min, under a stream of N_2, and then portions of DDQ (1.09 mol) were added over 10 min with stirring. The reaction mixture was heated under reflux for 5 h, evaporated *in vacuo* and treated with H_2SO_4 (1.40 M, 885 mL) at room temperature. After completion of the hydrolysis, the aqueous phase was extracted with CH_2Cl_2, followed by separation of organic and aqueous layers. The aqueous phase was adjusted to a basic pH by sodium hydroxide solution (40%), extracted with CH_2Cl_2 and then organic phase was distilled under reduced pressure to yield aniline (**9f**) as a colourless liquid; yield 72%; FTIR (KBr) (ν_{max} cm^{-1}): 3431, 3354 (N–H); ^1H NMR (400 MHz, $CDCl_3$): δ 7.29–7.24 (m, 2H), 6.90–6.85 (m, 1H), 6.76 (m, 2H), 3.67 (s, 2H).

Electronic Supplementary Information

The ESI containing infrared and ^1H NMR spectra is available through:
http://ingentaconnect.com/content/stl/jcr/2018/00000042/00000003/art00002

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