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Research Article

Synthesis of deuterium labelled 2-bromobenzylamine by directed *ortho*-metalation chemistry

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Summary

Directed *ortho*-metalation (DoM) strategy has been applied for the development of a short procedure for the regiospecific synthesis of [*phenyl*-$^2H_4$]-2-bromo-benzylamine **6** starting from commercially available [*phenyl*-$^2H_5$]-benzoyl chloride **1**. A strong isotope effect was observed during the *ortho*-substitution. Copyright © 2005 John Wiley & Sons, Ltd.

Key Words: 2-bromo-benzylamine; directed *ortho*-metalation; *N*-cumyl benzamide; deuterium; isotope effect

Introduction

[*Phenyl*-$^2H_4$]-2-bromobenzylamine **6** was required in our lab for the synthesis of internal standards in LC/MS assays in the development of a new series of Kv1.5 antagonists. Problems of site specificity during electrophilic substitution reactions of a suitable benzene derivative arise due to directing influence of the substituent already present in the aromatic substrate. [For a review of orientation and reactivity in benzene and other aromatic rings, see ref.[1]]. However, Sistrava *et al*. reported an example for regiospecific formation of an *ortho*-bromo substituted derivative even from substrates possessing *meta*-directing groups such as benzaldehyde.[2] More generally, regiospecific *ortho*-substitution can be achieved by the alternative approach of directed metalation strategy. [For a review on directed ortho metalation, see ref.[3]]. Various carboxamido groups have been shown to be powerful directed metalation groups (DMG) for the directed *ortho*-metalation (DoM) reaction.[4] Among them, *N*-cumyl benzamides showed certain advantages due to their strong directing influence combined with the mild conditions of cumyl

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deprotection, as demonstrated by Charette[5] and Snieckus.[6] Applying this method, we developed a short and convenient lab procedure for the synthesis of [*phenyl*-$^2H_4$]-2-bromo benzylamine **6**, starting from commercially available deuterium labelled benzoyl chloride **1**.

Results and discussion

[*Phenyl*-$^2H_5$]-benzoyl chloride **1** was treated with cumylamine to afford the deuterium labelled *N*-cumyl benzamide **2** in 91% yield (Figure 1). According to a procedure reported by Snieckus[6] initial experiments with unlabelled material furnished after lithiation and subsequent electrophile quench with 1,2-dibromo ethane the desired unlabelled 2-bromo *N*-cumyl benzamide **3** in 87% yield. The reaction proceeds smoothly without formation of side products and only traces of remaining starting material could be detected by TLC and NMR of the isolated product (Table 1, entry 1).

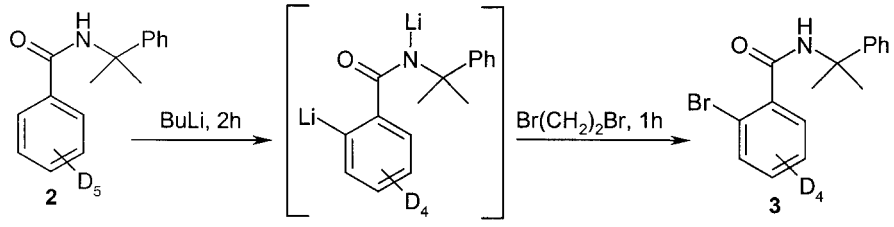
However, with (deuterated) **2** as substrate the reaction resulted in very low conversion of the starting material (Table 1, entry 2). For verification a 1:1 mixture of labelled and unlabelled benzamide **2** was treated under the same conditions to provide a 3:7 ratio of labelled and unlabelled product. Correspondingly, about 60% of remaining labelled benzamide **2** could be detected by NMR spectroscopic studies of the isolated mixture versus only 15% of unlabelled starting material. This fact clearly confirmed the occurrence of an isotopic effect during the metalation step. Though this kinetic isotope effect is basically known and deuterium has even been used as a protecting group to block *ortho*-lithiation,[7] the extent was surprising in view of the powerful metalation properties of the employed lithiation reagent.

Therefore, we undertook to optimize the metalation step. Variation of temperature as well as the type and equivalent amounts of the metalation reagent (Table 1, entry 3–7) were critical in increasing the yields of the reaction. In all attempts the reaction times (2 h for the metalation step and additional 1 h after electrophile quench) were kept constant.

In all cases the ratio of re-isolated benzamide **2** and product **3** was determined by ^{1}H-NMR-analysis of the isolated crude product mixture. Finally, best results could be achieved employing five equivalents of *s*-BuLi at -20°C (Table 1, entry 5). Due to difficult separation from unreacted **2**, the 2-bromo *N*-cumyl benzamide **3** was isolated as a mixture with **2** and used for the next synthesis step without further purification.

Decumylation of **3** was achieved with neat TFA at 50°C. The corresponding primary amides from **2** and **3** were easily separated by column chromatography to give pure bromo compound **4** in 59% yield based on **2**. Surprisingly, all attempts of direct reduction of the 2-bromo benzamide **4** to benzylamine **6** employing $LiAlH_4$, $LiAlH_4/AlCl_3$ or $BH_3 * SMe_2$ failed. However, going

Table 1. Optimization of metalation and electrophile quench reactions of *N*-cumyl benzamide 2



Entry	Reagent	Equiv. BuLi	Temperature	Ratio 2:3
1[a]	*s*-BuLi	3.5	−78°C	6:94
2	*s*-BuLi	3.5	−78°C	72:28
3	*s*-BuLi	3.5	−20°C	18:82
4	*s*-BuLi	3.5	0°C	40:60
5	*s*-BuLi	5.0	−20°C	14:86
6	*t*-BuLi	3.5	−78°C	75:25
7	*t*-BuLi	3.5	−20°C	90:10

[a] Reaction of unlabelled **2**.

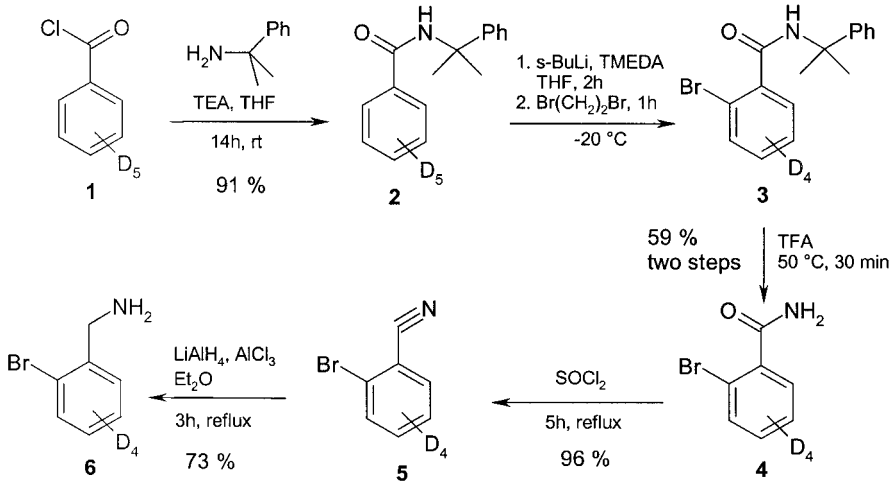


Figure 1. Synthesis of [*phenyl*-$^2H_4$]-2-Bromobenzylamine 6

through the nitrile **5**[†] which was easily prepared in nearly quantitative yield by treatment of **4** with thionyl chloride,[8] reduction was readily performed with $LiAlH_4/AlCl_3$ to afford the desired 2-bromo benzylamine **6** as the hydrochloride salt in 73% yield.

[†] According to the literature[6] the 2-bromo benzonitrile **5** should be also formed directly from *N*-cumyl amide **3** by the application of Charett's method[5] (Tf_2O/pyridine in CH_2C1_2, −40°C to 0°C/7 h, followed by addition of ethanol).

Experimental

General

All reagents were of commercial quality and were used as received. Cumylamine was purchased from ABCR and *s*-BuLi (1.3 M solution in cyclohexane/*n*-hexane 92/8) as well as *t*-BuLi (1.5 M solution in pentane) from Acros. Reactions were monitored by TLC, on aluminium sheets coated with silica gel with fluorescence indicator (silica gel 60 F_{254}, from Merck KGaA). Purifications by column chromatography were carried out on silica gel 60 (0.063–0.2 mm) from Merck KGaA with the described eluents. Melting points were measured with a Büchi 510 system and compared with available literature data. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker DRX 600 (600 MHz) nuclear magnetic resonance spectrometer. ^{1}H-NMR data were compared with literature data or checked against an authentic sample where possible. MS spectra were taken on a Bruker esquire 3000 mass spectrometer.

*[Phenyl-$^{2}H_5$]-N-cumyl benzamide (**2**).* 2.9 g (21.4 mmol) Cumylamine and 3.2 ml triethylamine were dissolved in 50 ml dry THF and 3.0 g (20.6 mmol) benzoyl chloride-[$^{2}H_5$] (Isotec, 99% deuterium) were added dropwise at rt. The reaction mixture was stirred at rt for 14 h (TLC-control, silica, ethyl acetate/*n*-heptane 1:1). Then 70 ml water and 50 ml ethyl acetate were added. The phases were separated and the aqueous phase was extracted three times with 50 ml ethyl acetate. The combined organic layers were washed two times with 50 ml water, dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. Yield: 4.6 g (18.8 mmol, 91%) colourless needles, mp 157°C. ^{1}H-NMR (600 MHz, DMSO-[D_6]) $\delta = 8.38$ (s, 1H), 7.38 (d, $^{3}J(H,H) = 7.88$ Hz, 2H), 7.27 (t, $^{3}J(H,H) = 7.7$ Hz, 2H), 7.16 (t, $^{3}J(H,H) = 7.1$ Hz, 1H), 1.66 (s, 6H) ppm; ^{13}C-NMR (150 MHz, DMSO-[D_6]) $\delta = 29.6$, 55.3, 124.6, 125.7, 127.0 (t, $^{1}J(C,D) = 24.4$ Hz), 127.5 (t, $^{1}J(C,D) = 24.3$ Hz), 127.9, 130.2 (t, $^{1}J(C,D) = 22.3$ Hz), 135.3, 148.0, 165.8; ESI-MS (%) *m/z*: 282.9 $[M + K]^+$ (4), 267 $[M + Na]^+$ (63), 244.9 $[M + H]^+$ (100).

*[Phenyl-$^{2}H_4$]-2-bromo N-cumyl benzamide (**3**).* 0.24 g (1.0 mmol) [*phenyl*-$^{2}H_5$]-*N*-cumyl benzamide **2** and 0.5 ml (3.3 mmol) TMEDA were dissolved in 10 ml dry THF under argon and cooled to −20°C. Then 3.8 ml (5.0 mmol) *s*-BuLi were added dropwise via syringe within 20 min, whereby the colour of the solution turned yellow. The solution was stirred for 2 h at −20°C and then 0.18 ml (2.2 mmol) 1,2-dibromo ethane was added dropwise at the same temperature. After completion of addition the resulting colourless solution was stirred for 1 h at −20°C (TLC-control, silica, ethyl acetate/*n*-heptane 1:1) and was then allowed to warm up to rt. Subsequently, 15 ml of saturated ammonium chloride solution and 15 ml toluene were added. The phases were separated and

the aqueous layer was extracted two times with 10 ml toluene. The combined organic layers were washed two times with 10 ml water and dried with Na_2SO_4. After filtration the solvent was removed *in vacuo* and the residue was dried to provide 0.28 g colourless solid of crude **3** (mixture of unreacted **2** and **3**, ratio see Table 1, entry 5), which was used for the next synthesis step without further purification. A small sample was purified by column chromatography on silica gel eluting with *n*-heptane/ethyl acetate 3:1. ^{1}H-NMR (600 MHz, DMSO-[D_6]) $\delta = 8.63$ (s, 1H), 7.47 (d, ^3J(H,H) = 7.42 Hz, 2H), 7.32 (t, ^3J(H,H) = 7.54 Hz, 2H), 7.20 (t, ^3J(H,H) = 7.36 Hz, 1H), 1.63 (s, 6H) ppm; ESI-MS (%) *m*/*z*: 343.8, 345.8 $[M + Na]^+$ (54), 321.8, 323.8 $[M + H]^+$ (100).

*[Phenyl-$^2H_4$]-2-bromo benzamide (**4**).* 0.28 g [*phenyl*-$^2H_4$]-2-bromo *N*-cumyl benzamide **3** (mixture with unreacted **2**) was treated with 5 ml trifluoric acetic acid and the resulting solution heated to 50°C. The progress of the reaction was monitored by TLC (*n*-heptane/ethyl acetate 1:1) indicating complete conversion after 1 h. After cooling to room temperature the pH was adjusted to pH 7 by the addition of 10 N NaOH whereupon a colourless waxy solid separated. This mixture was extracted three times with 10 ml ethyl acetate. The combined organic phases were dried with Na_2SO_4, filtered and the solvent removed *in vacuo*. The residue was purified by column chromatography on silica gel eluting with *n*-heptane/ethyl acetate 2:1. Selected fractions containing the product were pooled and concentrated in vacuo. Yield: 0.12 g (0.59 mmol, 59% starting from **2**) colourless solid, mp 162°C. ^{1}H-NMR (600 MHz, DMSO-[D_6]) $\delta = 7.83$ (s, br, 1H, NH), 7.54 (s, br, 1H, NH) ppm; ^{13}C-NMR (150 MHz, DMSO-[D_6]) $\delta = 118.9$, 127.6 (t, ^1J(C,D) = 24.8 Hz), 128.7 (t, ^1J(C,D) = 24.8 Hz), 130.5 (t, ^1J(C,D) = 23.9 Hz), 132.6 (t, ^1J(C,D) = 25.4 Hz), 139.8, 169.5 ppm; ESI-MS (%) *m*/*z*: 225.7, 227.7 $[M + Na]^+$ (63), 203.7, 205.7 $[M + H]^+$ (100).

*[Phenyl-$^2H_4$]-2-bromo benzonitrile (**5**).* 0.4 g (2.1 mmol) [*phenyl*-$^2H_4$]-2-bromo benzamide **4** was combined with 0.44 ml (6.0 mmol) thionyl chloride. The reaction mixture was heated to reflux and stirred for 5 h. The mixture was allowed to stand overnight at rt, whereby colourless needles precipitated. The crystals were filtered off, washed two times with *n*-heptane and finally dried *in vacuo*. Yield: 0.35 g (1.9 mmol, 96%) colourless needles, mp 56°C. ^{1}H-NMR (600 MHz, DMSO-[D_6]): no signals detected; ^{13}C-NMR (150 MHz, DMSO-[D_6]) $\delta = 114.8$, 117.7, 124.8, 128.6 (t, ^1J(C,D) = 25.3 Hz), 133.3 (t, ^1J(C,D) = 25.7 Hz), 135.1 (t, ^1J(C,D) = 25.8 Hz); ESI-MS (%) *m*/*z*: 204.7, 206.7 $[M + Na]^+$ (63), 185.7, 187.7 $[M + H]^+$ (100).

*[Phenyl-$^2H_4$]-2-bromobenzylamine hydrochloride (**6**).* Under inert atmosphere 0.15 g (4.0 mmol) lithium aluminium hydride powder was suspended in 5 ml of

dry diethyl ether. Then 0.53 g (4.0 mmol) aluminium chloride was added carefully in portions under stirring. The mixture was stirred for 10 min and then cooled to 0–5°C with an ice bath. Subsequently 0.37 g (2.0 mmol) [*phenyl*-$^2H_4$]-2-bromobenzonitrile **5** was added in small portions, whereby a gas evolution could be observed. After completion of addition the ice bath was removed and the reaction mixture stirred for 30 min at rt and subsequently heated to reflux for additional 3 h. The mixture was allowed to stay overnight at rt. The excess of lithium aluminium hydride was hydrolysed by addition of 2 ml of 2 N NaOH under cooling with an ice bath. The resulting solution was extracted three times with 10 ml diethyl ether. The combined organic phases were dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in 5 ml diethyl ether and 3 ml hydrogen chloride 1 M solution in diethyl ether were added. The resulting colourless precipitate was filtered off, washed with diethyl ether and dried *in vacuo*. Yield: 0.35 g (1.52 mmol, 73%) colourless solid, mp 227°C. ^{1}H-NMR (600 MHz, DMSO-[D_6]) $\delta = 8.59$ (s, br, 3H, NH), 4.22 (s, 2H, CH_2) ppm; ^{13}C-NMR (150 MHz, DMSO-[D_6]) $\delta = 41.9$, 123.1, 127.6, (t, ^1J(C,D) = 26.7 Hz), 130.2 (t, ^1J(C,D) = 25.2 Hz), 130.4 t, ^1J(C,D) = 25.2 Hz), 132.3 (t, ^1J(C,D) = 25.8 Hz), 133.2; ESI-MS (%) *m*/*z*: 189.7, 191.7 $[M(\text{-HCl}) + H]^+$ (86), 172.7, 174.7 $[M(\text{-HCl})\text{-}NH_2]^+$ (100).

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