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Research Article

Synthesis of benzoxazole-[phenyl-$^{13}C_6$] by directed *ortho*-metalation chemistry

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Summary

A new method for the preparation of benzoxazole-[phenyl-$^{13}C_6$] (**1**) starting from aniline-[$^{13}C_6$] (**4**) has been developed involving directed *ortho*-metalation (D*o*M) chemistry. The synthesis comprises four steps and an overall yield of 39% was obtained. Copyright © 2003 John Wiley & Sons, Ltd.

Key Words: benzoxazole; *ortho*-metalation; ^{13}C-labelling

Introduction

Benzoxazole (**1**) has been used as a building block in various pharmacologically relevant molecules as demonstrated by several examples in medicinal chemistry journals and the patent literature.[1] For the development of these potential drugs, pharmacokinetic studies with isotopically labelled material are necessary. The synthesis of specifically ^{13}C-labelled benzoxazole (**1**), as part of these potential drugs, becomes of interest as a result of the use of these labelled drug molecules as internal standard in LC/MS assays (Figure 1).

The retrosynthetic analysis of benzoxazole (**1**) suggests aminophenol (**2** and derivatives) as possible precursor. There are examples described in the literature wherein the ring-closure of aminophenol (**2**) was carried out using triazine or *ortho*-ester in moderate to good yields.[2] Aminophenol (**2**) could be prepared by two possible reaction pathways, through a nitration/reduction sequence starting from phenol (**3**) or by metalation/oxidation reaction starting from aniline (**4**). The nitration of phenols is frequently described in the literature, but in most cases a mixture of regioisomers was obtained.[3] The subsequent reduction of 2-nitrophenol was successfully performed under several reaction conditions with high yields.[4] Due to the low costs of the

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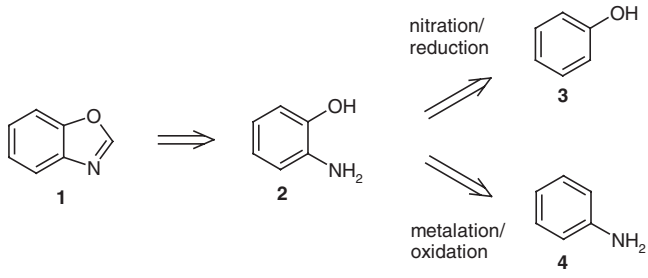


Figure 1. Retrosynthesis of benzoxazole

starting materials, most described syntheses are performed on multigram scale with distillations as the purification method which can be unfavourable on a small scale.

There are some examples of the directed *ortho*-lithiation of Boc-protected anilines,[5] but to our knowledge this method has not been used for the synthesis of aminophenol (**2**) yet. Therefore we developed a short and convenient lab procedure starting from aniline (**4**) using metalation chemistry for the introduction of substituents and chromatography as the purification method.

Results and discussion

Aniline-[$^{13}C_6$] (**4**) was Boc-protected by reaction with Boc-anhydride to give *N*-Boc-aniline-[phenyl-$^{13}C_6$] (**5**) in 91% yield (Figure 2). *N*-Boc-aniline-[phenyl-$^{13}C_6$] (**5**) was *ortho*-metalated[5] using *t*-BuLi (reactions with *n*-BuLi or *sec*-BuLi gave only minor metalation products as reported by[6]) and quenched with boronic ester to give, after aqueous workup, the boronic acid derivative as a crude product, which was directly converted into the phenol (**6**) by reaction with hydrogen peroxide. Over several attempts, we were able to increase the initially low yield of the reactions by variation of solvents and electrophiles (Table 1). A direct oxidation of the benzene–lithium species (**8**) with gaseous oxygen gave only inferior results (entries 6,7).[7] We finally performed the synthesis of ^{13}C-labelled *N*-Boc-aminophenol (**6**) as described in entry 2 (for details see experimental part) and isolated the desired product after purification by chromatography in 52% yield, while 31% of *N*-Boc-aniline-[phenyl-$^{13}C_6$] (**5**) was also recovered.

Best results for the deprotection of the amino function were achieved with TFA in dichloromethane (94% yield). Without further purification of aminophenol (**2**) the reaction with triazine (**7**) yielded benzoxazole-[phenyl-$^{13}C_6$] (**1**) as crude product which was purified by chromatography using pentane/diethylether as eluent to give (**1**) in 78% yield (purity $>98\%$).

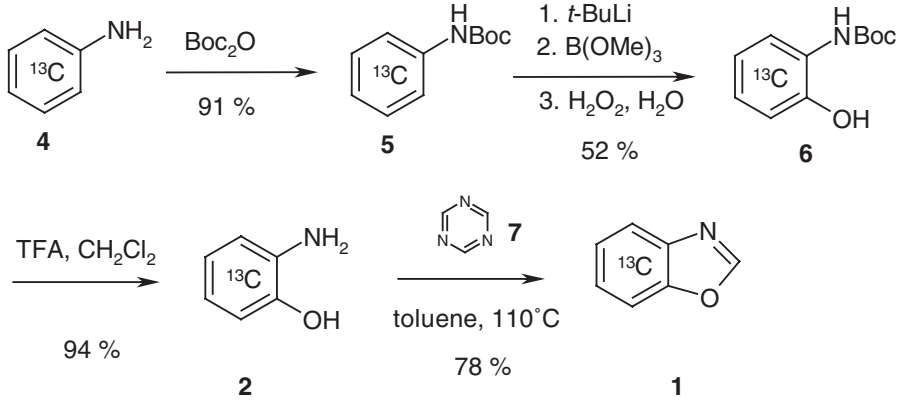
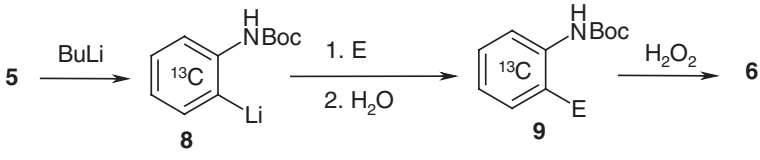
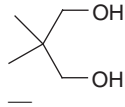


Figure 2. Metalation chemistry route for the synthesis of ^{13}C-benzoxazole

Table 1. Optimization of the metalation/oxidation reaction of *N*-Boc-aniline (5)



Entry	Reagent	Equiv	*E*	Additive	Solvent	5 [%]	6 [%]
1	*n*-BuLi	2.2	$B(OMe)_3$	—	THF	100	—
2	*t*-BuLi	3.3	$B(OMe)_3$	—	THF	31	52
3	*t*-BuLi	3.3	$B(OMe)_3$	—	Et_2O	14	47
4	*t*-BuLi	3.3	$B(OiPr)_3$	—	Et_2O	23	35
5	*t*-BuLi	3.3	$B(OiPr)_3$		Et_2O	43	32
6	*t*-BuLi	3.3	O_2	—	Et_2O	74	8
7	*t*-BuLi	3.3	O_2	$Ti(OiPr)_4$	Et_2O	65	11

Experimental

General

The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker 500 and 600 nuclear magnetic resonance spectrometers. ^{13}C-decoupled ^{1}H-NMR experiments were accomplished and compared with literature data or an authentic sample if possible. The purification of the compounds was done on open columns with silica gel 60 (Merck) and the eluents described. The purity analyses were performed on a Gilson HPLC system using a Luna C18 RP column with an acetonitrile/water gradient as mobile phase. *t*-BuLi was purchased from Aldrich and used directly.

N-Boc-aniline-[phenyl-$^{13}C_6$] (5). 26.5 g (0.12 mol) Boc-anhydride was added into a 250 ml round bottom flask flushed with argon. The solid was dissolved in 10 ml chlorobenzene and 10.0 g (0.10 mol) aniline-[$^{13}C_6$] (**4**) (CDN isotopes, 99% isotopically pure) was added in portions at room temperature. The reaction mixture was heated to 50°C for 1 h and to 80°C for a further 36 h. Then methylcyclohexane (10 ml) was added and the solution allowed to cool to room temperature. The reaction mixture was centrifuged, the colourless solid was washed twice with 5 ml methylcyclohexane and dried in vacuo to give 18.4 g (92.4 mmol, 91%) *N*-Boc-aniline-[phenyl-$^{13}C_6$] (**5**) as colourless needles (>97% purity). Identity was checked by comparison with an authentic sample purchased from Aldrich using a ^{1}H-NMR (^{13}C-decoupled) spectrum.[8]

2-N-Boc-aminophenol-[phenyl-$^{13}C_6$] (6). 4.54 g (22.8 mmol) *N*-Boc-aniline-[phenyl-$^{13}C_6$] (**5**) was introduced into a 250 ml round bottom flask and the flask flushed with argon for 10 min. After addition of 60 ml dry THF the solid was dissolved and the solution cooled to –78°C. Then, 46.9 ml (70.0 mmol) *t*-BuLi were added dropwise via syringe (15 min) and stirred for 15 min. The solution was allowed to come up to –20°C and stirred for a further 2 h. After addition of 7.04 ml (62 mmol) trimethylborate the solution was stirred for 8 h at room temperature. Then, 8 ml water was added, the phases separated and the aqueous phase extracted three times with 20 ml dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent removed in vacuo. The oily residue was dissolved in 7.9 ml ethanol/water (1:1) and cooled to 0°C. After dropwise addition of 7.9 ml hydrogen peroxide (30% in water) the solution was stirred at room temperature for two hours. The aqueous phase was extracted 5 times with 20 ml dichloromethane, the combined organic phases dried over anhydrous Na_2SO_4 and the solvent removed in vacuo. The crude product was purified by silica gel chromatography (heptane/ethyl acetate 4:1) to give 2.57 g (12.3 mmol, 52%) of (**6**) (purity 94%) and 1.37 g (7.09 mmol, 31%) of recovered starting material (**5**). ^{13}C-decoupled ^{1}H-NMR spectra of (**6**) are in accordance with literature data.[9]

2-Aminophenol-[$^{13}C_6$] (2). 3.35 g (15.6 mmol) 2-*N*-Boc-aminophenol-[phenyl-$^{13}C_6$] (**6**) were dissolved in 14 ml dichloromethane/TFA (1:1) and stirred at room temperature for 1 h (TLC-control, silica, dichloromethane/MeOH 2:1). After addition of 1 ml TFA the solution was stirred for one additional hour. Subsequently 2 N NaOH solution was added at 0°C to give a solution of pH 8. The aqueous phase was extracted 2 times with 30 ml dichloromethane and 2 times with 20 ml ethyl acetate. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent removed in vacuo to give 1.69 g (14.7 mmol, 94%) of (**2**) as a brown solid (>93% purity by HPLC, contained

4% TFA as determined by ^{19}F-NMR). ^{13}C-decoupled ^{1}H-NMR spectra of (**2**) are in accordance with literature data.[4b,c]

Benzoxazole-[phenyl-$^{13}C_6$] (1). 1.74 g (15.1 mmol) Aminophenol-[$^{13}C_6$] (**2**) were suspended in 9 ml dry toluene and 253 mg (3.12 mmol) 1,3,5-triazine (Merck) (**7**) and 2.2 ml triethylamine added. The reaction mixture was heated to reflux for 15 h and a further 84 mg (1.00 mmol) 1,3,5-triazine and 1.0 ml triethylamine added. After 3 h reflux the reaction mixture was cooled to room temperature and 3.5 ml water added. The phases were separated, the organic layer dried over anhydrous Na_2SO_4 and directly purified by open column silica gel chromatography using pentane/ether 5:1 as mobile phase. The relevant fractions were combined and the solvent removed by short path distillation (bath temperature should not exceed 55°C). Traces of residual solvent were evaporated in vacuo (30–45 s) to give 1.47 g (11.8 mmol, 78%) of (**1**) as a colourless oil which crystallizes after a few hours (99% purity). ^{1}H-NMR (600 MHz, MeOD) $\delta = 8.49$ (dd, $J = 4.8$ Hz, $J = 4.8$ Hz, 1 H), 7.92–7.82 (m, 1 H), 7.64–7.55 (m, 2 H), 7.35–7.28 (m, 1 H); ^{1}H-NMR (600 MHz, MeOD, ^{13}C decoupled) $\delta = 8.47$ (s, 1 H), 7.77 (d, $J = 7.8$ Hz, 1 H), 7.69 (d, $J = 7.8$ Hz, 1 H), 7.48–7.41 (m, 2 H); in accordance with literature data[2d]; ^{13}C-NMR (150 MHz, $CDCl_3$) $\delta = 154.1$ (ratio 1:100, N = CH–O), 150.5–149.4 (m, 1C_q), 140.6–139.5 (m, 1C_q), 126.1–124.0 (m, 2CH), 121.1–120.1 (m, 1CH), 111.4–110.4 (m, 1CH) ppm.

Conclusion

We have developed a short synthesis for benzoxazole-[phenyl-$^{13}C_6$] (**1**) based on a common ^{13}C-starting material. The synthesis of aminophenol-$^{13}C_6$ (**2**) by metalation chemistry has been optimized to obtain 52% yield as the best result.

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