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Benzo[*b*]thiophene as a template for substituted quinolines and tetrahydroquinolines

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Abstract—An original methodology starting from 3-aroyl-2-(2′-nitro-4′-methoxyphenyl)-benzo[*b*]thiophene allows the synthesis of unusual fused heterocycles. Direct hydrogenation with nickel catalysts followed by desulfurisation led to 2,3-diarylquinolines or 2,3-diaryltetrahydroquinolines.

1. Introduction

The development of new methods for the synthesis of nitrogen or sulfur-containing heterocycles is of importance in medicinal chemistry. Among these structures, quinolines,[1] tetrahydroquinolines[2] and their derivatives are excellent precursors of potential drugs.[3] Quinolines are usually synthesised by cyclisation reactions[4] and, to our knowledge, methods that allow the direct synthesis of 2,3-diarylated quinolines are rare.[4b,c] Little work has addressed the synthesis of 2,3-disubstituted tetrahydroquinolines by intermolecular[5] or intramolecular[6] cyclisation. Usually, the methods involve the hydrogenation of the quinoline precursors, either by PtO_2,[7] Pd/C[8] or nickel complexes.[5a]

In this letter, we present a simple and efficient synthetic methodology starting from the benzo[*b*]thiophene scaffold to form, in a few steps, a number of various heterocyclic structures. We investigated the synthesis of rare polycyclic compounds such as 11-thia-5-aza-benzo[*a*]-fluorenes **4a**–**c** (or benzothieno[3,2-*c*]quinolines) and their N-oxide derivatives **3a**–**c**. As far as we know, only one compound functionalised at the alpha position of the nitrogen was synthesised in four steps.[9]

2. Results and discussion

We have recently reported the direct arylation at position 2 of the benzo[*b*]thiophene core by palladium coupling.[10] In the presence of a $Pd(OAc)_2/PPh_3$ system and potassium carbonate as a base, 2-(2′-nitro-4′-methoxyphenyl)-benzo[*b*]thiophene **1** was obtained in 62% yield. Acylation at position 3 yielded 3-aroyl-2-(2′-nitro-4′-methoxyphenyl)-benzo[*b*]thiophenes **2a**–**c** in good yields (74–91% yield). Hydrogenation of the nitro group afforded an amine, which condensed on the ketone group and cyclised into the corresponding benzothieno[3,2-*c*]quinolines **4a**–**c**.

Although no biological evaluation was performed on these structures, their nitrogen bioisosteres, indolo[3,2-*c*]-quinolines proved to possess potent antimalarial activity and were generally synthesised in 5–7 steps.[11] Finally, desulfurisation of benzothieno[3,2-*c*]quinolines **4a**–**c**, followed by hydrogenation led to 2,3-diarylated quinolines or tetrahydroquinolines **5a**–**c** (Scheme 1).

The reduction of the nitro group was performed with Raney nickel under an inert or hydrogen atmosphere (Table 1). It was found that, at room temperature and under an atmosphere of argon, partial hydrogenation

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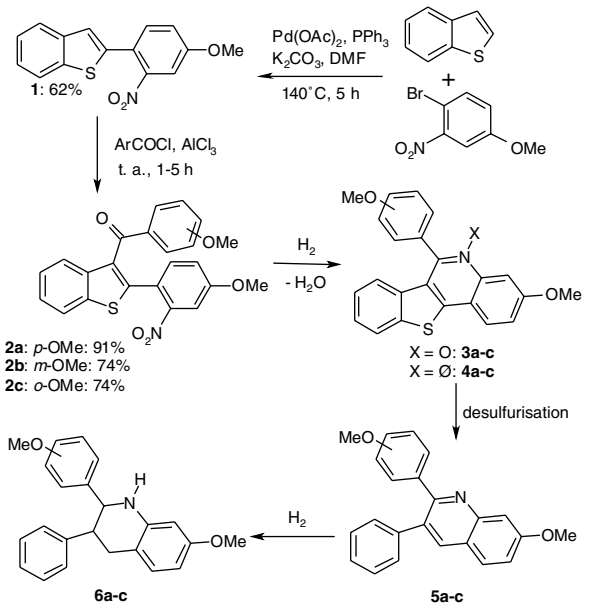


Scheme 1.

occurred, yielding benzothieno[3,2-*c*]quinolines-N-oxides **3a–c** isolated in moderate yields (Table 1, entries 1, 4 and 7). This phenomenon was described recently for the hydrogenation/cyclisation of a nitro group.[12] The authors speculated that partial hydrogenation yielded a hydroxylamine, which as in our case, is reactive enough to condense on the ketone group.

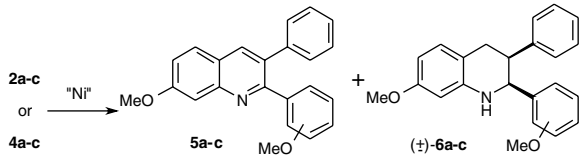
Under 1 bar of hydrogen, a 30:1 ratio of Raney nickel/substrate was required for the synthesis of benzo[*b*]thieno[3,2-*c*]quinolines **4a–c**, which were obtained in moderate yields (entries 2, 5 and 8). However, the reaction afforded improved yields at higher temperature and higher hydrogen pressure (30 atm) with 1.5 equiv of Raney nickel (Table 1, entries 3, 6 and 9). Under these conditions, a large excess of Raney nickel yielded partial degradation of the product into the corresponding desulfurised compounds. Indeed, Jones reported that Raney nickel could be used to desulfurise 2-arylbenzo[*b*]thiophenes.[13] However, the drawbacks of Raney nickel are numerous as they are tedious to prepare, difficult to weigh accurately and require a large Ni/S ratio.[14a] We turned our attention to other nickel systems, NiCRA's[14] and Ni_2B[15] (Table 2), which are known for their high efficiency and chemoselectivity in the desulfurisation of polyaromatic sulfur-containing compounds.

No cyclisation was observed when performed with NiCRA catalyst on compounds **2a–c** (Table 2, entries 1, 4 and 7). Indeed NiCRA catalysts have never been reported as good reducing agents. In addition, this type of catalyst is known for its high selectivity towards desulfurisation, preventing any further hydrogena-

Table 1. Hydrogenation of compounds **2a–c** with Raney nickel

Entry	Substrate **2**	Atm	Temperature (°C)	Time (h)	Product **3** (%)	Product **4** (%)
1	**a**	Ar	20	2	**51**	17
2		1 atm H_2	20	24	—	74
3		30 atm H_2	100	2	—	**88**
4	**b**	Ar	20	2	**49**	23
5		1 atm H_2	20	24	—	59
6		30 atm H_2	100	4	—	**90**
7	**c**	Ar	20	24	**27**	<10
8		1 atm H_2	20	48	—	74
9		30 atm H_2	100	6	—	**78**

Table 2. Desulfurisation study of compounds **2a–c** and **4a–c**



Entry	Substrate	Catalyst	Time (h)	Product **5** (%)	Product **6** (%)
1	**2a**	Ni Raney	24	—	**6a** 60
2	**2a**	Ni_2B	24	—	**6a** 56
3	**4a**	NiCRA's	15	**5a** 66	—
4	**2b**	Ni Raney	24	—	**6b** 19
5	**2b**	Ni_2B	48	—	**6b** 38
6	**4b**	NiCRA's	15	**5b** 52	**6b** 6
7	**2c**	Ni Raney	24	**5c** 12	**6c** 26
8	**2c**	Ni_2B	24	—	**6c** 38
9	**4c**	Ni_2B	5	—	**6c** 35
10	**4c**	NiCRA's	60	**5c** 48	—

tion.[14a] To our delight, desulfurisation of compounds **4a**–**c** afforded the corresponding quinolines **5a**–**c** in good yields and with very little quantities of by-products (Table 2, entries 3, 6 and 10).

On the other hand, the Ni_2B system was reported as an efficient reagent for the reduction of nitro compounds, desulfurisation and hydrogenation of the quinoline ring. However, hydrogenation of the benzo[*b*]thieno-quinoline **4c** to the corresponding tetrahydroquinoline **6c** gave only a moderate yield of 35% (Table 2, entry 9). When the synthesis of tetrahydroquinolines **6a**–**c** was investigated from the non-cyclised compounds **2a**–**c**, similar results were obtained either with Raney nickel (Table 2, entries 1, 4 and 7) or with Ni_2B (Table 2, entries 2, 5 and 8).

A yield of 38–60% appeared to be quite satisfactory considering the number of steps involved in this one-pot synthesis (reduction, cyclisation, desulfurisation then hydrogenation). In addition, the tetrahydroquinolines were isolated as only one pair of enantiomers. The cis or trans configuration at C_2 and C_3 was determined by ^{1}H NMR on compound **6a**. It was found that H-2 was correlated with H-3 in a coupling constant J_{H2H3} of 4 Hz in agreement with 2,3-*cis*-disubstituted tetrahydroquinolines H-2/H-3 coupling constants previously reported.[8] This low value prevents the protons from adopting an axial–axial conformation as described in a recent paper where a 2,3,4-(*trans*,*trans*)-trifunctionalised tetrahydroquinoline gave a 10 Hz H-2/H-3 coupling constant.[5b] Based on a 2D NOESY experiment, the comparative study of the interproton distances from cross peak amplitudes[16] confirmed the cis configuration of **6a** with a distance H2–H3 of 230 pm.

3. Conclusion

In conclusion, we have developed a rapid and efficient methodology for the synthesis of unusual fused heterocycles.[17] A one-pot hydrogenation/desulfurisation afforded the corresponding quinolines and tetrahydroquinolines. The latter are the first *cis*-2,3-diarylated tetrahydroquinolines described by NMR so far. Recent experiments confirmed that this original methodology can be extended to a wide variety of sulfur-containing substrates as well as functional groups. Considerable efforts along these lines are currently in progress.

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17. *3-Methoxy-6-(4-methoxy-phenyl)-11-thia-5-aza-benzo[a]-fluorene-5-oxide* **3a**: In a round bottom flask filled with Raney nickel (15 mmol) in ethanol (5 mL) was added compound **2a** (210 mg; 0.5 mmol) and the mixture was stirred at room temperature for 2 h. Dichloromethane (10 mL) was added to dissolve the yellow precipitate and the mixture was filtered prior to evaporation. The resulting solid was purified by flash chromatography (silica, cyclohexane/AcOEt 90:10) to afford compound **3a** (98 mg; 51%) as a pale yellow powder; mp >270 °C. Anal. Found: C 71.10, H 4.47, N 3.61, O 12.51. Calcd for $C_{23}H_{17}NO_3S$: C 71.30, H 4.42, N 3.61, O 12.39; δ_H (300 MHz, $CDCl_3$) 3.96 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 6.83 (d, 1H, *J* 8.3 Hz), 7.15 (ddd, 1H, *J* 1.1; 7.3; 8.1 Hz), 7.19 (d, 2H, *J* 8.7 Hz), 7.33 (dd, 1H, *J* 2.5; 8.9 Hz), 7.36 (ddd, 1H, *J* 1.1; 7.3; 8.3 Hz), 7.50 (d, 2H, *J* 8.7 Hz), 7.84 (d, 1H, *J* 8.1 Hz), 7.96 (d, 1H, *J* 8.9 Hz), 8.30 (d, 1H, *J* 2.5 Hz); δ_C (75 MHz, $CDCl_3$) 55.5 (CH_3), 56.0 (CH_3), 100.7 (CH), 115.1 (2CH), 119.0 (C), 121.5 (CH), 122.8 (CH), 124.5 (CH), 125.0 (C), 125.1 (CH), 126.0 (CH), 126.4 (C), 126.7 (CH), 130.7 (2CH), 134.7 (C), 136.1 (C), 138.9 (C), 140.8 (C), 143.7 (C), 160.6 (C), 161.9 (C) ppm; *m/z* 389 (20), 388 (MH^+, 100), 370 (50), 327 (10); HRMS EI found: 387.0924, calcd for $C_{23}H_{17}NO_3S^{+\cdot}$: 387.0929.

3-Methoxy-6-(2-methoxy-phenyl)-11-thia-5-aza-benzo[a]-fluorene **4c**: To Raney nickel (0.75 mmol) in ethanol was added compound **2c** (210 mg; 0.5 mmol) and the mixture was stirred in a hydrogen pressurised (30 atm) reactor at 100 °C for 2 h. Dichloromethane (10 mL) was added to dissolve the white precipitate and the mixture was filtered prior to evaporation. The resulting solid was purified by flash chromatography (silica, cyclohexane/AcOEt 95:5) to afford compound **4c** (145 mg; 78%) as an amorphous white powder; mp 149–150 °C. Anal. Found: C 74.37, H 4.71, N 3.70, O 8.67. Calcd for $C_{23}H_{17}NO_2S$: C 74.37, H 4.61, N 3.77, O 8.61; δ_H (300 MHz, $CDCl_3$) 3.63 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 7.06 (ddd, 1H, *J* 0.7; 1.2; 8.1 Hz), 7.11 (d, 1H, *J* 8.3 Hz), 7.19 (ddd, 1H, *J* 1.1; 7.2; 8.3 Hz), 7.20 (ddd, 1H, *J* 1.1; 7.4; 7.5 Hz), 7.30 (dd, 1H, *J*2.5; 9.0 Hz), 7.38 (ddd, 1H, *J* 1.1; 7.2; 8.2 Hz), 7.47 (dd, 1H, *J* 1.8; 7.5 Hz), 7.56 (ddd, 1H, *J* 1.8; 7.4; 8.1 Hz), 7.69 (d, 1H, *J* 2.5 Hz), 7.91 (ddd, 1H, *J* 0.7; 1.1; 8.1 Hz), 8.04 (d, 1H, *J* 9.0 Hz); δ_C (75 MHz, $CDCl_3$) 55.7 (CH_3), 55.7 (CH_3), 108.9 (CH), 111.3 (CH), 118.4 (C), 119.6 (CH), 121.5 (CH), 122.7 (CH), 123.8 (CH), 125.0 (CH), 125.1 (CH), 126.0 (CH), 126.9 (C), 130.1 (C), 130.1 (CH), 130.5 (CH), 135.8 (C), 138.5 (C), 146.5 (C), 147.1 (C), 154.5 (C), 157.3 (C), 160.8 (C) ppm; *m/z* 371 (M^+, 60), 340 (50), 297 (60), 266 (100), 207 (10); HRMS CI found: 372.1054, calcd for $C_{23}H_{17}NO_2SH^+$: 372.1058.

7-Methoxy-2-(3-methoxy-phenyl)-3-phenyl-quinoline **5b**: 3-Hydroxy-1-methylpiperidine (2 mmol) in 2 mL dried THF was added dropwise to a suspension of NaH (7 mmol) and $Ni(OAc)_2$ (1 mmol) in hot THF (6 mL). After 1 h of reflux, the substrate **4b** (74 mg; 0.2 mmol) was added dropwise in THF (2 mL). After 15 h stirring at 65 °C, the crude mixture was cooled to 20 °C and ethanol (1 mL) and water (15 mL) were added. The mixture was extracted three times with dichloromethane (20 mL), and the combined organic phases were dried over $MgSO_4$, filtered and evaporated. The crude products were purified by flash chromatography (silica, heptane/ethyl acetate 98:2) to afford compound **5b** (35 mg; 52%) as a pale beige solid; mp 113–114 °C. Anal. Found: C 80.51, H 5.66, N 3.89, O 8.95. Calcd for $C_{23}H_{19}NO_2$: C 80.92, H 5.61, N 4.10, O 9.37; δ_H (300 MHz, $CDCl_3$) 3.67 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 6.87 (ddd, 1H, *J* 0.9; 2.6; 8.2 Hz), 7.02 (dd, 1H, *J* 1.5; 2.6 Hz), 7.06 (ddd, 1H, *J* 0.9; 1.5; 7.7 Hz), 7.20 (dd, 1H, *J* 7.7; 8.2 Hz), 7.24 (dd, 1H, *J* 2.4; 9.0 Hz), 7.25–7.32 (m, 5H), 7.47 (d, 1H, *J* 2.4 Hz), 7.76 (d, 1H, *J* 9.0 Hz), 8.11 (s, 1H); δ_C (75 MHz, $CDCl_3$) 55.2 (CH_3), 55.7 (CH_3), 107.4 (CH), 114.6 (CH), 115.0 (CH), 120.2 (CH), 122.6 (C), 122.7 (CH), 127.0 (CH), 128.3 (2CH), 128.6 (CH), 129.1 (CH), 129.8 (2CH), 132.5 (C), 137.4 (CH), 140.3 (C), 141.9 (C), 149.0 (C), 158.3 (C), 159.2 (C), 161.0 (C) ppm; *m/z* 341 (M^+, 40), 340 (100), 325(20), 297 (30), 254 (20); HRMS CI found: 342.1496, calcd for $C_{23}H_{19}NO_2H^+$: 342.1494.

7-Methoxy-2-(4-methoxy-phenyl)-3-phenyl-1,2,3,4-tetrahydro-quinoline **6a**: Compound **2a** (1 mmol) and $NiCl_2{\cdot}6H_2O$ (15 mmol) were dissolved in methanol (35 mL) and THF (15 mL) in an opened flask cooled in an ice bath. The solution was stirred while $NaBH_4$ (45 mmol) was added in small portions. After stirring under 30 bar hydrogen pressure at 100 °C for the time indicated, the crude mixture was filtered over a short pad of silica. The metallic residue was treated with a 1 M solution of HCl (50 mL) and extracted with dichloromethane (50 mL). The aqueous solution was basified with a 1 M KOH solution and then extracted with dichloromethane (50 mL). The combined organic phases were dried over $MgSO_4$, filtered and added to the first filtrate prior to evaporation. The crude product was purified by flash chromatography (silica, heptane/ethyl acetate 99.5:0.5) to afford compound **6a** (193 mg; 56%) as an amorphous white solid; mp 132–134 °C. Anal. Found: C 79.76, H 6.77, N 3.91, O 9.60. Calcd for $C_{23}H_{23}NO_2$: C 79.97, H 6.71, N 4.05, O 9.26; δ_H (500 MHz, $CDCl_3$) 3.00 (d, 2H, *J* 7.5 Hz), 3.49 (dt, 1H, *J* 4.0; 7.5 Hz), 3.75 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.32 (br s, 1H, NH), 4.66 (d, 1H, *J* 4.0 Hz), 6.20 (d, 1H, *J* 2.5 Hz), 6.33 (dd, 1H, *J* 2.5; 8.3 Hz), 6.66 (d, 2H, *J* 8.9 Hz), 6.72 (d, 2H, *J* 8.9 Hz), 6.84–6.89 (m, 2H), 6.99 (d, 1H, *J* 8.3 Hz), 7.15–7.20 (m, 3H); δ_C (75 MHz, $CDCl_3$) 29.2 (CH_2), 44.1 (CH), 55.6 (CH_3), 55.6 (CH_3), 60.1 (CH), 99.3 (CH), 103.5 (CH), 113.3 (2CH), 113.6 (C), 126.8 (CH), 128.2 (2CH), 129.1 (2CH), 129.2 (2CH), 130.5 (CH), 134.2 (C), 141.9 (C), 145.6 (C), 159.0 (C), 159.6 (C) ppm; *m/z* 345 (M^+, 40), 254 (100), 224 (30); HRMS CI found: 346.1805, calcd for $C_{23}H_{23}NO_2H^+$: 346.1807.