Pergamon

Tetrahedron 56 (2000) 8567–8571

TETRAHEDRON

Unexpected Dealkylation During Nucleophilic Substitution: Synthesis of 2-*N*,*N*-Dialkylamino Benzoxazoles and Benzothiazoles

Abedawn I. Khalaf,[a,*] Ricardo G. Alvarez,[a] Colin J. Suckling[a] and Roger D. Waigh[b]

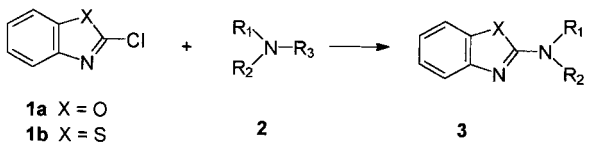
[a]*Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow G1 1XL, Scotland, UK*
[b]*Department of Pharmaceutical Sciences, Strathclyde Institute for Biomedical Sciences, 27 Taylor Street, Glasgow G4 0NR, Scotland, UK*

Received 6 July 2000; revised 18 August 2000; accepted 30 August 2000

Abstract—Mild reaction conditions are described for the preparation of a number of 2-alkyl- and 2-arylaminobenzoxazoles and benzothiazoles from 2-chlorobenzoxazole and 2-chlorobenzothiazole and *N*-methyl or other simple *N*-alkyl tertiary amines. The reaction proceeds neat or in THF solution and involves dealkylation of the amine reactant by nucleophilic substitution by chloride. In the case of *N*-methylpyrrolidine and *N*-methylpiperidine demethylation was not observed and the major product was formed by ring opening to give chlorobutyl- and chloropentyl-methylamino substituted benzoxazoles and benzothiazoles. Treatment of the chlorobutyl derivative with iodide in acetone afforded the new 1*H*,2*H*,3*H*,4*H*,5*H*-[1,3]diazepino[2,1-*b*][1,3]benzoxazol-6-ium ring system.

As part of a programme of synthesis into minor groove binders for DNA,[1] we required to prepare distamycin analogues with heterocyclic head groups. Accordingly 2-chlorobenzoxazole was reacted with a distamycin analogue precursor that bore both a primary and a tertiary amine. Surprisingly, substitution to afford the corresponding aminobenzoxazole occurred at both amino groups with concomitant demethylation or de-ethylation of the tertiary amine.[2–6] This unexpected reaction of the tertiary amines prompted us to investigate the generality of the reaction. Although the products of these reactions, *N*,*N*-dialkylamino benzoxazoles and benzothiazoles, have been prepared before,[10–12] most recently using high pressure,[4] (see Table 1 for further references) the reactions described here offer simpler and more direct routes to these compounds.

Treatment of 2-chlorobenzoxazole (**1a**) with *N*-methylmorpholine (**2a**) under reflux in THF (or neat at 130°C) afforded 2-*N*-morpholinobenzoxazole (**3a**) in good yield (85%) after purification through a short column. In THF solution, 2-chlorobenzothiazole (**1b**) was much less reactive giving the corresponding morpholinothiazole (**3b**) in only 8% yield. However in the absence of solvent a significantly increased yield (50%) was obtained. Concentration and temperature therefore seem to be important in this new reaction.



1a X = O
1b X = S

2 **3**

The scope of this substitutive dealkylation reaction was studied to examine the influence of ring alkyl substitution in the tertiary amines. *N*,*N*-Dimethylbenzylamine underwent substitution with loss of the benzyl group to give **3d** (87%) but *N*,*N*-dimethylaniline afforded 2-*N*-methyl-*N*-phenylbenzoxazole (**3f**) in moderate yield (43%) with loss of the methyl group. Triethylamine reacted similarly to the other trialkylamines giving the diethylamino derivative **3e** in 89% yield. On the other hand, dicyclohexylmethylamine and *N*,*N*-diethylaniline failed to react. These results and others (Table 1) show that the normal effects of reactivity in nucleophilic substitution are followed. Attack of the nucleophile on the aryl halide is subject to steric hindrance and substitution is preferred at benzylic sites.

The reaction mechanism suggested by these observations (Scheme 1) involves initial addition of the tertiary amine to the heteroaryl chloride giving an adduct with a positively charged nitrogen atom. Instead of chloride acting as a leaving group, the adduct decomposes by nucleophilic substitution with the quaternary ammonium salt acting as a leaving group. Once chloride has been formed in the aprotic reaction mixture, it is a potential nucleophile leading to alkyl chlorides as the by-products. Benzyl chloride was indeed detected from the ^{1}H NMR signal at δ 4.6 in the

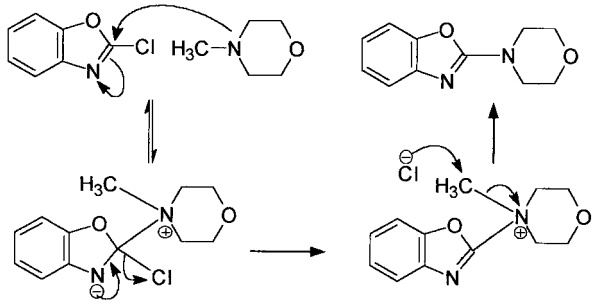
Keywords: 2-arylaminobenzoxazoles; 2-chlorobenzoxazole; 2-chlorobenzothiazole; dealkylation; [1,3]diazepino[2,1-b][1,3]benzazoles.
* Corresponding author. Tel.: +141-548-2271; fax: +141-548-4733; e-mail: c.j.suckling@strath.ac.uk

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00802-4

Table 1. Synthesis of **3** from 2-chlorobenzoxazole (or 2-chlorobenzothiazole) and tertiary amines

Entry	Product	X	R^1	R^2	R^3	Yield%	Mp (°C)
1	**3a**	O	Morpholino		CH_3	80	92–95[a]
2	**3b**	S	Morpholino		CH_3	50	122–125[b]
3	**3c**	O	CH_3	CH_3	CH_2Ph	87	89–91[c]
4	**3d**	S	CH_3	CH_3	CH_2Ph	72	84–86[d]
5	**3e**	O	CH_2CH_3	CH_2CH_3	CH_2CH_3	89	Oil[4,15]
6	**3f**	O	CH_3	Ph	CH_3	43	Oil[8]
7	**3g**	O	Pyrrolidino		CH_3	7[e]	134–135[f]
8	**3h**	S	Pyrrolidino		CH_3	7[e]	96–98[g]
9	**3i**	O	Piperidino		CH_2CH_3	86	72–73[h]
10	**3j**	S	Piperidino		CH_2CH_3	41	90–91[i]
11	**3k**	S	CH_3	Ph	CH_3	17	Oil[j]

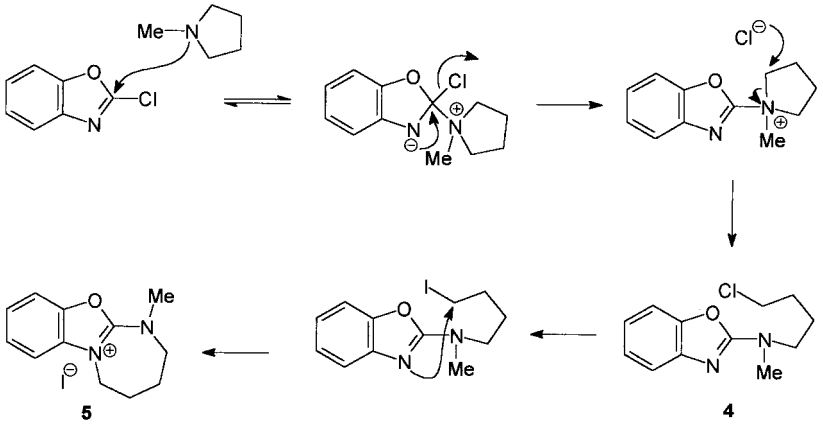
[a] Lit.[13] mp 88–89°C.
[b] Lit.[14] mp 126–127°C.
[c] Lit.[13] mp 88–89°C.
[d] Lit.[13] mp 84–86°C.
[e] Indicates that the major product was a ring opened derivative (see below).
[f] Lit.[9] mp 136–137°C.
[g] Lit.[16] mp 98–100°C.
[h] Lit.[17] mp 70–71°C.
[i] Lit.[7] mp 93–95°C.
[j] Lit.[18] mp 66–67°C.



Scheme 1. Proposed mechanism of dealkylative substitution.

reaction mixture with benzyldimethylamine as substrate and the increase of the alkyl chloride was followed during the course of the reaction. The action of chloride and bromide as nucleophiles in substitution reactions of ammonium salts, sulphonium salts, and oxonium salts is well known. It is also possible that attack by chloride on the methyl group is internal, i.e. the two stages are concerted, a reasonable suggestion because of the proximity of the departing chloride and the adjacent polarised C–N bond.

A further unusual observation was made. When the products of the reactions of 2-chlorobenzoxazole and 2-chlorobenzothiazole with *N*-methylpyrrolidine or *N*-ethylpyrrolidine were purified, a second product was isolated along with the expected adducts **3g** and **3h**. The new products contained covalently bound chlorine and the methyl group was still present; they were insoluble in water and clearly not salts. In the case of the compound derived from *N*-methylpyrrolidine, high resolution mass spectroscopy established the molecular formula $C_{14}H_{19}ClN_2O$. The ^{13}C NMR spectrum showed four distinct methylene groups deriving from the pyrrolidine ring suggesting that the ring opened structure **4** (Scheme 2) represented the new compound. This suggestion was also consistent with the long range couplings shown by COSY experiments: an interaction between the *N*-methyl protons (δ 3.20) and the methylene protons (δ 3.68) was observed. What is not easily understood is that this reaction is strongly favoured in the case of pyrrolidine. A small amount of the analogous product was characterised from the reaction of *N*-ethylpiperidine and 2-chlorobenzoxazole but in other cases no ring cleavage product was detected, although it may have been present in small quantity. Again, it is possible that



Scheme 2. Proposed mechanism of formation of ring opened products and further cyclisation.

release of chlorine from the oxazole ring and attack on the pyrrolidine carbon is a concerted process, which may be sterically favoured in the five-membered ring. To confirm the presence of the chloromethyl group, compound **4** was treated with sodium iodide in acetone at room temperature. This surprisingly led to the formation of a new fused heterocyclic system, 1-Methyl-1*H*,2*H*,3*H*,4*H*,5*H*-[1,3]diazepino[2,1-*b*][1,3]benzoxazol-6-ium iodide, **5**. Evidence for this structure comes from the water solubility of **5** and the downfield shift of the methylene protons (δ_H 3.68–4.02 and 4.48) and carbons (δ_C 44.48 and 49.55–47.14 and 54.48) and *N*-methyl protons (δ_H 3.20–3.50) and carbons (δ_C 35.42–41.97). Symmetrical structures such as pyrrolidinium salts are ruled out (Scheme 2).

Recently, further reactions under high pressure have been described for the preparation of 4-dialkyl-aminopyridines.[19] It would be interesting to discover whether milder conditions such as those described here would be successful in that case also.

Experimental

The majority of compounds prepared by the new route have been described before. Physical constants for compounds obtained and literature comparisons are given in Table 1. Spectroscopic data are reported below with the preparative details. IR spectra: solids were run as KBr discs and liquids as films, using a Nicolet Impact 400D. Low- and high-resolution (EI-MS) mass spectra were obtained on a Jeol JMS-AX505HA mass spectrometer. NMR spectra were obtained on a Bruker AMX 400 spectrometer operating at 400 MHz for ^{1}H and 100.6 MHz for ^{13}C. Column chromatography was performed with silica gel Prolabo (200–400 mesh).

2-*N*-morpholinobenzoxazole (3a).[13] *N*-Methylmorpholine (329 mg, 3.256 mmol) was dissolved in THF (20 mL, dry) to which 2-chlorobenzoxazole (504 mg, 3.256 mmol) was added at room temperature with stirring. The reaction mixture was heated under reflux for 3 h then the solvent removed under reduced pressure at 50°C. The residue was dissolved in a small amount of ethyl acetate and applied to a silica gel column. Ethyl acetate/*n*-hexane (1:1 v/v) was used to elute the product, which was obtained as a pale yellow solid (529 mg, 80%); δ_H ($CDCl_3$): 3.62–3.65 (4H, t, *J*=4.8 Hz, CH_2–N–CH_2); 3.83–3.86 (4H, t, *J*=4.8 Hz, CH_2–O–CH_2); 7.06 (1H, dt, *J*=1.2 and 7.8 Hz, Ar*H*); 7.19 (1H, dt, *J*=1.2 and 7.8 Hz, Ar*H*); 7.26 (1H, d, *J*=7.8 Hz, Ar*H*); 7.38 (1H, d, *J*=7.8 Hz, Ar*H*). ν_{max}: 1670, 1580, 1461, 1290, 1108, 763, 744 cm^{-1}.

2-*N*,*N*-dimethylaminobenzoxazole (3c).[13] *N*,*N*-Dimethylbenzylamine (507 mg, 3.750 mmol) and 2-chlorobenzoxazole (576 mg, 3.750 mmol) were heated at 130°C for 3 h. The reaction mixture was left to cool to room temperature then the crystalline mass was dissolved in hot ethyl acetate and applied to a silica gel column. The required benzoxazole (**3c**) was obtained as white crystalline material by elution with ethyl acetate/*n*-hexane (1:1 v/v) (527 mg, 87%). δ_H ($CDCl_3$): 3.21 (6H, s, NMe_2); 7.00 (1H, dt, *J*=1.2 and 7.7 Hz, Ar*H*); 7.16 (1H, dt, *J*=1.2 and 7.8 Hz, Ar*H*); 7.25 (1H, d, *J*=7.8 Hz, Ar*H*); 7.36 (1H, d, *J*=7.8 Hz, Ar*H*). δ_C ($CDCl_3$): 37.65, 108.55, 115.98, 120.16, 123.82, 143.58, 149.07, 163.05. ν_{max}: 1665, 1588, 1462, 1426, 901, 745 cm.$^{-1}$

Similarly the following compounds were prepared.

2-*N*-Morpholinobenzothiazole (3b).[14] As a pale yellow crystalline solid (50%); δ_H ($CDCl_3$): 3.64 (4H, t, *J*=4.8 Hz, CH_2NCH_2); 3.85 (4H, t, *J*=4.7 Hz, CH_2OCH_2); 7.11 (1H, dt, *J*=1.2 and 7.4 Hz, Ar*H*); 7.32 (1H, dt, *J*=1.2 and 7.4 Hz, Ar*H*); 7.58 (1H, d, *J*=7.4 Hz, Ar*H*); 7.62 (1H, d, *J*=7.4 Hz, Ar*H*). ν_{max}: 1596, 1562, 1539, 1443, 1291, 1116, 759, 727 cm^{-1}. HREIMS: found 220.066. Calculated for $C_{11}H_{12}N_2OS$ 220.067.

2-*N*,*N*-Dimethylaminobenzothiazole (3d).[13] As a white crystalline solid (72%). δ_H ($CDCl_3$): 3.21 (6H, s, NMe_2); 7.06 (1H, dt, *J*=1.2 and 7.4 Hz, Ar*H*); 7.29 (1H, dt, *J*=1.2 and 7.4 Hz, Ar*H*); 7.57 (1H, d *J*=7.4 Hz, Ar*H*); 7.60 (1H, d, *J*=7.4 Hz, Ar*H*). δ_C ($CDCl_3$): 40.40, 118.99, 120.81, 121.10, 126.13, 131.34, 153.47, 168.99. ν_{max}: 1599, 1574, 1546, 1453, 1416, 1295, 750, cm^{-1}.

2-*N*,*N*-Diethylaminobenzoxazole (3e).[4,15] As a colourless oil (89%). δ_H ($CDCl_3$): 1.27–1.31 (6H, t, *J*=7.1 Hz, NCH_2CH_3); 3.57–3.62 (4H, q, *J*=7.1 Hz, NCH_2CH_3); 6.96–7.01 (1H, dt, *J*=1.1 and 7.8 Hz, Ar*H*); 7.12–7.16 (1H, dt, *J*=1.1 and 7.8 Hz, Ar*H*); 7.25 (1H, d, *J*=7.8 Hz, Ar*H*); 7.36 (1H, d, *J*=7.8 Hz, Ar*H*). δ_C ($CDCl_3$): 13.44, 42.91, 108.45, 115.77, 119.89, 123.73, 143.65, 148.81, 162.20. ν_{max}: 2968, 2937, 1647, 1580, 1466, 1399, 1251, 784, 761, 748 cm^{-1}.

2-*N*-Methyl-*N*-phenylaminobenzoxazole (3f).[8] As a colourless oil (43%). δ_H ($CDCl_3$): 3.64 (3H, s, N*Me*); 7.03–7.08 (1H, dt, *J*=1.1 and 7.8 Hz, Ar*H*); 7.18–7.22 (1H, dt, *J*=1.1 and 7.7 Hz, Ar*H*); 7.25–7.31 (2H, m, Ar*H*); 7.42–7.48 (5H, m, Ar*H*). δ_C ($CDCl_3$): 39.04, 108.94, 116.66, 121.07, 123.99, 124.43, 126.02, 129.24, 142.76, 142.95, 148.74, 161.26. ν_{max}: 3063, 2940, 1632, 1570, 1503, 1380, 1246, 1138, 755, 747, 701 cm^{-1}.

Reaction of *N*-methylpyrrolidine and (1a): formation of *N*-(4-chlorobutyl)-*N*-methylaminobenzoxazole. 2-Chlorobenzoxazole (460 mg, 3.0 mmol) and *N*-methylpyrrolidine (260 mg, 3.0 mmol) were dissolved in THF (20 mL, dry). The reaction mixture was heated under reflux for 6 h. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica eluted with ethyl acetate/*n*-hexane (1:20 v/v). The first fraction (compound of type **4**, *N*-(4-chlorobutyl)-*N*-methylaminobenzoxazole) was obtained as a colourless oil (617 mg, 86%). δ_H ($CDCl_3$): 1.85 (4H, m, $(CH_2)_2CH_2N$); 3.20 (3H, s, N*Me*); 3.68 (4H, m, CH_2Cl and CH_2N); 7.01 (1H,dt, *J*=1.2 and 7.8 Hz, Ar*H*); 7.15 (1H, dt, *J*=1.2 and 7.8 Hz, Ar*H*); 7.26 (1H, d, *J*=7.8 Hz, Ar*H*); 7.36 (1H, d, *J*=7.8 Hz, Ar*H*). δ_C ($CDCl_3$): 24.78, 29.48, 35.42, 44.48, 49.55, 108.55, 115.96, 120.18, 123.85, 143.45, 148.85, 162.65. ν_{max}: 2956, 2867, 1598, 1567, 1544, 1447, 1293, 753, 727 cm^{-1}. HREIMS: found 238.087, calculated for $C_{12}H_{15}N_2O^{35}Cl$ 238.087, and found 240.086 calculated for $C_{12}H_{15}N_2O\ ^{37}Cl$ 240.086.

The second fraction was obtained as white solid material (40 mg, 7%), identified as **3g**.[9] δ_H ($CDCl_3$): 2.05 (4H, t, J=8 Hz, $(CH_2)_2CH_2N$); 3.66 (4H, t, J=4.0 Hz, CH_2N); 6.99 (1H, t, J=7.8 Hz, Ar*H*); 7.15 (1H, t, J=7.8 Hz, Ar*H*); 7.26 (1H, d, J=7.8 Hz, Ar*H*); 7.36 (1H, d, J=7.8 Hz, Ar*H*). δ_C ($CDCl_3$): 25.58, 47.40, 108.55, 115.95, 120.04, 123.81, 143.58, 149.00, 160.98. ν_{max}: 2922, 1642, 1584, 800, 760, 740 cm^{-1}.

Reaction of *N*-ethylpiperidine and (1a): *N*-(4-chloropentyl)-*N*-ethylaminobenzoxazole. 2-Chlorobenzoxazole (460 mg, 3.0 mmol) and 1-ethylpiperidine (679 mg, 6.0 mmol) were dissolved in THF (20 mL, dry). The reaction mixture was heated under reflux for 24 h. The solvent was removed under reduced pressure and the residue purified by column chromatography eluted with ethyl acetate/*n*-hexane (1:9 v/v). The first fraction was obtained as a white solid which was identified as **3i**,[17] (519 mg, 86%). δ_H ($CDCl_3$): 1.73 (6H, m, 3×CH_2); 3.71 (4H, m, CH_2N); 7.04 (1H, dt, J=1.2 and 7.8 Hz, Ar*H*); 7.19 (1H, dt, J=1.2 and 7.8 Hz, Ar*H*); 7.28 (1H, d, J=7.8 Hz, Ar*H*); 7.39 (1H, d, J=7.8 Hz, Ar*H*). δ_C ($CDCl_3$): 24.08, 25.24 (2×C); 46.62 (2×C); 108.54, 116.00, 120.26, 123.82, 143.39, 148.71, 162.47. ν_{max}: 2941, 2854, 1643, 1576, 1454, 1275, 792, 754, 743 cm^{-1}. A second fraction (compound of type **4**, *N*-(4-chloropentyl)-*N*-ethylaminobenzoxazole) was obtained as a colourless oil (55 mg, 7%). δ_H ($CDCl_3$): 1.27–1.31 (3H, t, J=7.1 Hz, CH_2CH_3), 1.49–1.58 (2H, m, CH_2), 1.69–1.77 (2H, m, CH_2), 1.82–1.89 (2H, qt, J=6.7 Hz, CH_2), 3.51 (2H, t, J=7.4 Hz, CH_2N), 3.53 (2H, t, J=6.7 Hz, CH_2Cl), 3.57 (2H, q, J=7.3 Hz, NCH_2CH_3), 6.99 (1H, dt, J=1.2 and 7.8 Hz, Ar*H*), 7.15 (1H, dt, J=1.2 and 7.8 Hz, Ar*H*), 7.27 (1H, d, J=7.8 Hz, Ar*H*), 7.34 (1H, d, J=7.8 Hz, Ar*H*). δ_C ($CDCl_3$): 13.29, 24.09, 27.54, 32.30, 43.47, 44.80, 48.01, 108.53, 115.89, 120.04, 123.83, 148.82, 162.47. ν_{max}: 2939, 1649, 1585, 1462, 760, 745 cm^{-1}. HREIMS: found 266.119, calculated for $C_{14}H_{19}N_2O^{35}Cl$ 266.119; and found 268.116, calculated for $C_{14}H_{19}N_2O^{37}Cl$ 268.116.

Reaction of (1b) with *N*-methylpyrrolidine: formation of *N*-(4-chlorobutyl)-*N*-methylaminobenzothiazole. The same experimental procedure as above was employed to give two products eluted with ethyl acetate/petroleum ether (1:3 v/v). The first fraction (compound of type **4**, *N*-(4-chlorobutyl)-*N*-methylaminobenzothiazole) was obtained as a colourless oil (83%). δ_H ($CDCl_3$): 1.82–1.85 (4H, m, 2×CH_2), 3.18 (3H, s, N*Me*), 3.56–3.59 (4H, m, NCH_2 and CH_2Cl), 7.06 (1H, dt, J=1.2 and 7.8 Hz, Ar*H*), 7.29 (1H, dt, J=1.2 and 7.8 Hz, Ar*H*), 7.55 (1H, d, J=7.8 Hz, Ar*H*), 7.59 (1H, d, J=7.8 Hz, Ar*H*). δ_C ($CDCl_3$): 24.84, 29.84, 38.14, 44.78, 52.47, 118.97, 120.77, 121.14, 126.13, 131.04, 153.37, 168.50. ν_{max}: 2956, 2867, 1598, 1544, 1447, 1293, 754, 727 cm^{-1}. HREIMS: found 254.065 calculated for $C_{12}H_{15}N_2S^{35}Cl$ 254.064; and found 256.063 calculated for $C_{12}H_{15}N_2S^{37}Cl$ 256.063. The second fraction (**3h**) was obtained as a white solid (7%).[16] δ_H ($CDCl_3$): 2.05 (4H, t, J=8.0 Hz, 2×CH_2); 3.66 (4H, t, J=4.0 Hz, 2×NCH_2); 7.03–7.06 (1H, dt, J=1.1 and 7.8 Hz, Ar*H*); 7.27–7.31 (1H, dt, J=1.1 and 7.8 Hz, Ar*H*); 7.57–7.61 (2H, m, Ar*H*). δ_C ($CDCl_3$): 25.88, 49.71, 118.91, 120.88, 126.12, 131.96, 153.55, 165.58. ν_{max}: 2922, 1642, 1583, 1459, 761 cm^{-1}.

2-Piperidinobenzothiazole (3j). 2-Chlorobenzothiazole (504 mg, 2.971 mmol) and *N*-ethylpiperidine (1.009 g, 8.913 mmol) were heated at 130°C for five days. Excess reagent was removed under reduced pressure and the crude product was applied to a column chromatography. Ethyl acetate/*n*-hexane 1/10 was used to elute the product which was obtained as pale yellow crystalline material (**3j**) (266 mg, 41% yield), R_f=0.33. δ_H ($CDCl_3$): 1.68 (6H, br s, 3×CH_2); 3.56 (4H, br s, CH_2NCH_2); 7.03–7.07 (1H, dt, J=1.1 and 7.8 Hz, Ar*H*); 7.26–7.31 (1H, dt, J=1.1 and 7.8 Hz, Ar*H*); 7.55–7.59 (2H, m, Ar*H*). δ_C ($CDCl_3$): 24.67, 25.71 (2×C), 50.02 (2×C), 119.21, 120.97, 121.44, 126.26, 131.12, 153.42, 169.25. ν_{max}: 2945, 2924, 2846, 1593, 1561, 1535, 1444, 1261, 762, 732 cm^{-1}.

2-*N*-methyl-*N*-phenylaminobenzothiazole (3k).[18] The same procedure for the synthesis of (**3f**) was employed to give the product as a colourless oil. δ_H ($CDCl_3$): 3.66 (3H, s, N*Me*); 7.09 (1H, dt, J=1.1 and 7.8 Hz, Ar*H*); 7.30–7.52 (7H, m, Ar*H*); 7.66 (1H, d, J=7.8 Hz, Ar*H*). δ_C ($CDCl_3$): 40.59, 119.36, 120.60, 121.88, 126.00, 126.12 (2×C), 127.55, 130.06 (2×C), 131.33, 145.96, 152.78, 168.37. ν_{max}: 3063, 1593, 1521, 755 cm^{-1}.

1-Methyl-1*H*,2*H*,3*H*,4*H*,5*H*-[1,3]diazepino[2,1-*b*][1,3]benzoxazol-6-ium iodide (compound of type 5). *N*-(4-chlorobutyl)-*N*-methylaminobenzoxazole (20 mg, 0.084 mmol) was dissolved in dry acetone (5 mL) to which was added anhydrous sodium iodide (25 mg, 0.10 mmol). The solution was heated under reflux for 8 h and allowed to cool to room temperature. The sodium chloride precipitate was filtered and the solvent evaporated to dryness under reduced pressure, to afford the product as a white solid (25 mg, 90%). mp>240°C. δ_H ($CDCl_3$): 2.27–2.39 (4H, m, 2×CH_2), 3.50 (3H, s, N*Me*), 4.02 (2H, t, J=5.6 Hz, NCH_2), 4.48 (2H, t, J=5.6 Hz, N^+CH_2), 7.31–7.36 (1H, m, Ar*H*), 7.39–7.47 (3H, m, Ar*H*). δ_C ($CDCl_3$): 24.60, 24.42 (CH_2–CH_2), 41.97 (N*Me*), 47.14 (NCH_2), 54.48 (N^+CH_2), 111.46, 111.91, 125.54, 126.67 (CH of Ar), 131.92, 144.35 (C of Ar), 158.6 (N^+=*C*–O(N)). HRFABMS Found 203.11834 (95%, base peak), calculated for $C_{12}H_{15}N_2O$ 203.11844 (M^+-I^-). ν_{max} 1685, 1480, 1400, 1267, 1164, 758 cm^{-1}.

Acknowledgements

The authors would like to acknowledge the grant gratefully received by R. G. A. from the D.G.U.I. (Gobierno de Canarias).

References

1. (a) Khalaf, A. I.; Pitt, A. R.; Scobie, M.; Suckling, C. J.; Urwin, J.; Waigh, R. D.; Young, S. C.; Fishleigh, R. V.; Fox, K. R. *J. Med. Chem.* in press. (b) Khalaf, A. I.; Pitt, A. R.; Scobie, M.; Suckling, C. J.; Urwin, J.; Waigh, R. D.; Young, S. C.; Fishleigh, R. V. *Tetrahedron* **2000**, *56*, 5225–5239. (c) Khalaf, A. I.; Pitt, A. R.; Scobie, M.; Suckling, C. J.; Urwin, J.; Waigh, R. D.; Young, S. C.; Fishleigh, R. V. *J. Chem. Res., Synopsis* **2000**, 246–265; *J. Chem. Res., Miniprint* 0751–0770.

2. Brown, H. C. *J. Am. Chem. Soc.* **1945**, *67*, 378–380.

3. (a) Miller, J. *Aromatic Nucleophilic Substitution*; Elsevier: Amsterdam, 1968. (b) Bacaloglu, R.; Blasko, A.; Bunton, C. A.;

Dorwin, E.; Ortega, F.; Zucco, C. *J. Am. Chem. Soc.* **1991**, *113*, 238–246.
4. Matsumoto, K.; Hashimoto, S.; Otani, S. *J. Chem. Soc., Chem. Commun.* **1991**, 306–307.
5. Kukhar, V. P. *J. Org. Chem. USSR (Engl. Transl.)* **1978**, *14*, 1710–1714.
6. Hervens, F.; Viehe, H. G. *Angew. Chem., Int. Ed. Engl.* **1973**, *12* (5), 405–406 (see also 1991).
7. Nagarajan, K.; Kulkarni, C. L.; Shah, R. K. *Indian J. Chem.* **1971**, *9*, 748–754.
8. Matsumoto, K.; Toda, M.; Hashimoto, S. *Chem. Lett.* **1991**, *8*, 1283–1286.
9. Hetzheim, A.; Schlaak, G.; Kerstan, C. *Pharmazie* **1987**, *42* (2), 80–82.
10. Elderfield, R. C.; Green, M. *J. Org. Chem.* **1952**, *17*, 431–441.
11. Hunziker, F.; Schindler, O. *Helv. Chim. Acta* **1965**, *48*, 1590–1597.
12. Davidkov, K.; Simov, D. *Dokl. Bolg. Akag. Nauk.* **1968**, *21* (11), 1193–1196 (*Chem. Abstr.* 70:57714k).
13. Benassi, R.; Grandi, R.; Pagnoni, U. M.; Taddei, F. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1513–1522.
14. Da'mico, J. J.; Webster, S. T.; Campbell, R. H.; Twine, C. E. *J. Org. Chem.* **1965**, *30*, 3618–3625.
15. Advani, S. P.; Sam, J. *J. Pharm. Sci.* **1968**, *57*, 1693–1696.
16. Claude, S.; Tabacchi, R.; Duc, L.; Fuchs, R.; Boosen, K. *Helv. Chim. Acta* **1980**, *63* (3), 682–692.
17. Eilingsfeld, H.; Moebius, L. *Chem. Ber.* **1965**, *98*, 1293–1307.
18. D'Amico, J. J.; Tung, C. C.; Walker, L. A. *J. Am. Chem. Soc.* **1959**, *81*, 5957–5959.
19. Kotsuki, H.; Sakai, H.; Shinohara, T. *Synlett* **2000**, 116–118.