A NOVEL SYNTHESIS OF 3,3-(SPIRO)SUBSTITUTED AZETIDINES

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Abstract - A smooth and efficient new synthesis for 3,3-disubstituted azetidines, starting from readily available nitriles, was established: α-hydroxymethylation of the starting materials, followed by *O*-tosylation and $LiAlH_4$-reduction of the key intermediates thus obtained, led - *via* spontaneous cyclization of the intermediate amino derivatives - to 3,3-disubstituted azetidines. Scope and limitations of this new method were studied with respect to generalized applicability: the target compounds were accessible in good yields for a variety of starting materials (cyclic and acyclic di(hetero)aryl, (hetero)arylalkyl, dialkyl, as well as basic moieties). The products thus obtained may be of interest for ensuing conversions due to their unblocked nitrogen.

Dedicated to Prof. Katritzky with very best wishes

INTRODUCTION

Some general strategies for syntheses of azetidines are based on intramolecular cyclizations of bi-functional open-chain precursors,[1, 2] utilizing γ-halogenated amines, γ-aminoalkylsulfonates and 1,3-diamines or 1,3-dihalides as starting materials.

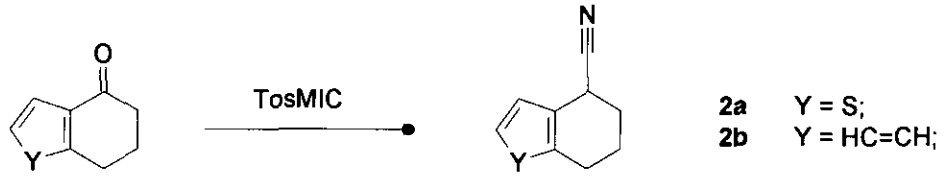
Recently published methods involve dehydration of *N*-alkylated amino alcohols with triphenylphosphonium dibromide/Et_3N[3] or triphenylphosphine/CCl_4/Et_3N,[4] anodic oxidation of α-(ω-tosylaminoalkyl)malonates[5] and reduction of β-chloro-*N*-substituted imines.[6]

Within our ongoing research dealing with the syntheses of various (hetero-)spiro systems[7] a new smooth and efficient method for preparing azetidines was developed by converting β-hydroxy nitriles to *O*-tosylated intermediates, which subsequently were reduced with $LiAlH_4$ and cyclized *in situ*.

RESULTS AND DISCUSSION

Starting Materials

The preparation of the nitriles (**2a - h**) used as starting materials was effectuated from ketones (**1a-h**) (all **1b**[8] being commercial products) by two different methods: **2a,b** and **2d-h** were prepared *via* a variation of the TosMIC method according to Oldenziel[9] as published in one of our papers[10] as depicted in *Scheme 1*.

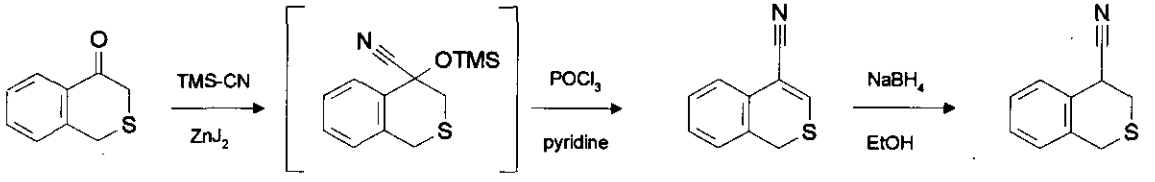


1a Y = S;
1b Y = HC=CH;

2a Y = S;
2b Y = HC=CH;

Scheme 1

A different method[11] had to be applied to isothiochromanone (**1c**) (for which the TosMIC procedure was inapplicable) according to *Scheme 2*: in this case trimethylsilyl cyanide was added to **1c**, subsequent elimination of the TMS-*O*-moiety with $POCl_3$/pyridine and reduction of the olefinic intermediate (**7c**) with $NaBH_4$ gave the desired nitrile (**2c**):

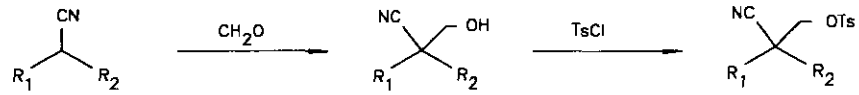


1c **7c** **2c**

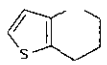
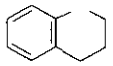
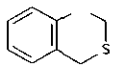
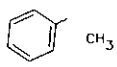
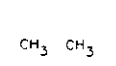
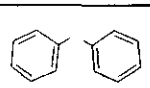
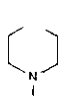
Scheme 2

Synthesis of Azetidines (5a-h)

According to *Table 1* α-deprotonation of the starting nitriles (**2a-h**) (by LDA or Triton B) and reaction with gaseous formaldehyde gave hydroxylmethyl derivatives (**3a-h**) which subsequently were tosylated in pyridine or methylene chloride/triethylamine to yield the target compounds (**4a-h**).



2a-h **3a-h** **4a-h**

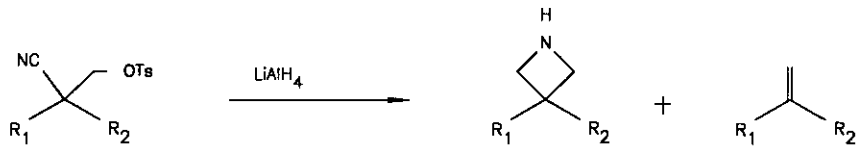
2	R_1,R_2	method	T (°C)	time	3	yield (%)	4	yield (%)
a		B	20	3 d	**a**	80	**a**	84
b		A	-60	2 h	**c**	65	**c**	83
c		A	-40	1.5 h	**b**	77	**b**	76
d		A	-40	1 h	**d**	50[12]	**d**	54
e		A	-40-0	2 h	**e**	58[12]	**e**	31
f		A	-35	1 h	**f**	48[12]	**f**	48
g		B	20	2 h	**g**	98	**g**	76
h		A	30	4 h	**h**	72	**h**	65

Method A: LDA/CH_2O Method B: Triton B/CH_2O

Table 1

The tosylate (**4a**) was originally intended to be reduced to an amino alcohol: while this was effected in low yield by $BH_3.SMe_2$, reaction with $LiAlH_4$ surprisingly gave reduction and cyclization in an one

pot reaction yielding 80% of azetidine (**5a**). Since this overall sequence turned out to be a new method to synthesize 3,3-disubstituted azetidines, its scope and limitations were studied. A variety of starting ketones (**1a-h**) with different steric and electronic properties were chosen to investigate the general applicability of this method. The reaction conditions applied and the results obtained are summarized in *Table 2*.



4a-h **5a-h** **6a-h**

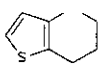
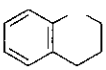
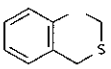
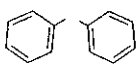
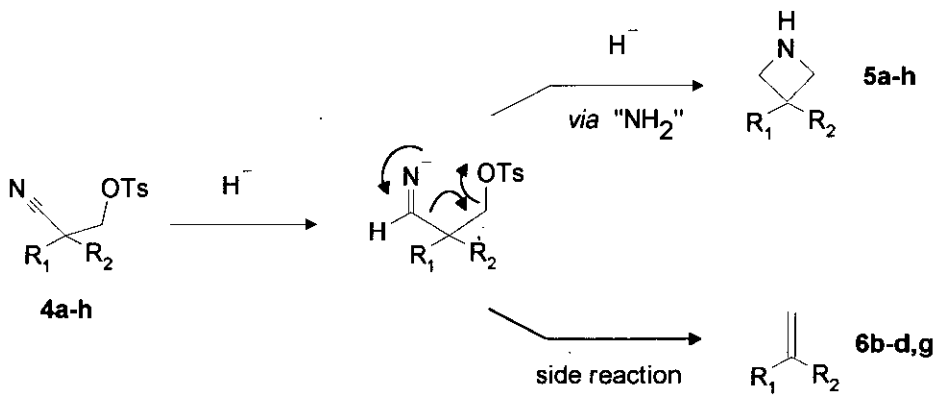
4	R_1, R_2	solvent	temp.	time	**5** (%)	**6** (%)
a		THF	25° C	1 h	80	-
b		THF	15° C 25° C	1 h	76 65	- 10
c		Et_2O	20° C	3.5 h	46	24
d		THF	19° C	1 h	72[13]	5
e		THF	20° C	2 h	82[13a])	-
f		Et_2O	24° C	0.7 h	90[14]	-
g		THF	20° C	2 h	41[13]	50
h		THF	35° C	1 h	80	-

Table 2 (references refer to first citation in literature *via* different strategy)

*) isolated as *N*-tosylate

The target compounds (**5a-b, 5d-f** and **5h**) could be obtained in good yields ranging from 72-90% (based on Kugelrohr-distilled or recrystallized compounds). In some cases (**5c**, **5d** and **5g, 5b** only at elevated temperatures) signals of an olefinic by-product (**6**) were observed in nmr spectra of the crude reaction products. Due to their apolar nature these compounds could be removed easily by filtration over silica gel (the yields given for **6** in *Table 2* refer to material isolated from such operations).

Such elimination products only occurred when a conjugated π-system could be formed. As demonstrated with compound (**4b**), lowered reaction temperature disfavoured its formation. The high amount of **6g** (50%) may be due to the presence of a highly conjugated π-system, whereas the increased amount of **6c** compared to that of **6b** might be explained by an additional sulfur 1,3-neighbouring-group effect. The formation of the olefins (**6**) may be rationalized - according to *Scheme 3* - as an elimination reaction competing with further hydride transfer and subsequent cyclization of the intermediate amino-*O*-tosylate moiety to yield the targets (**5a-h**).



Scheme 3

CONCLUSION

The reaction sequence discussed above turned out to be a new, short and efficient route to 3,3-disubstituted azetidines obtained from readily available ketones or nitriles, applicable to a wide range of different substituents. By this means four new spiro-compounds (**5a, 5b, 5c** and **5h**) were sythesized. An additional advantage offered by this method is the presence of an unsubstituted nitrogen, enabling smooth access to a variety of *N*-substituted azetidines.

EXPERIMENTAL

The melting points given were determined on a Kofler melting point apparatus and are uncorrected. Elementary analyses were performed at the Microanalytical Laboratory, Institute of Physical Chemistry, University of Vienna (Mag. J. Theiner). Tlc: Tlc-layers with SiO_2 60 F_{254}, Merck Art.-Nr. 5554; eluents: petroleum ether (PE); ethyl acetate (EA); triethylamine (TEA). "Flash"-chromatography: SiO_2 60 F_{254}, Merck Art.-Nr. 9385, particle size: 0.040-0.063 mm, pressure: 1 bar; 50 g SiO_2 in 450 x 25 mm glass columns. ^{13}C- and ^{1}H-nmr-spectra: Bruker AC 200 (^{1}H: 200.13 MHz, ^{13}C: 50.47 MHz), 5 mm dual $^{1}H/^{13}C$-VT-probe head at 300 K; solvent: DMSO-d_6 and $CDCl_3$, respectively; δ-values are given ppm, internal standard TMS (δ = 0 ppm); THF and ether were dried by distillation over Na/benzophenone; 2.5 m BuLi / n-hexane, 1 molar $LiAlH_4$-solution in ether or THF, trimethylsilyl cyanide, anhydrous ZnI_2 and Triton B (40% in MeOH) were purchased from Aldrich.

1H-2-Benzothiopyran-4-carbonitrile (7c): 1H-2-Benzothiopyran-4(3H)-one (4.93 g, 30 mmol) and TMSCN (4.5 ml, 36 mmol), together with a catalytic amount of anhydrous ZnI_2 (50 mg), were stirred under N_2 atmosphere in 10 ml of dry benzene for 24 h at 55°C yielding the TMS-O-intermediate. After removal of the solvent $POCl_3$ (13.8 g, 90 mmol) and 60 ml of pyridine were added and the reaction mixture was heated to 110°C for 3 days. Work-up with 3N HCl (650 ml), extraction with ether, evaporation and Kugelrohr distillation yielded 2.52 g (48%) of **7c** as yellowish crystals, mp 62-65°C; bp (Kugelrohr) 60-65°C (0.02 mm Hg); Rf = 0.7 (PE/EA=3:1); ^{1}H-nmr ($CDCl_3$): δ 7.65-7.50 (m, 1H), 7.44-7.30 (m, 3H), 7.18-7.10 (m, 1H), 3.91 (s, 2H); ^{13}C-nmr ($CDCl_3$): δ 140.8 (d), 129.7 (d), 128.3 (s), 128.1 (d), 127.1 (d), 125.2 (s), 124.6 (d), 116.6 (s), 108.9 (s), 29.5 (t); Anal. Calcd for $C_{10}H_7NS$: C, 69.05; H, 4.10; N, 8.05. Found: C, 69.09; H, 4.23; N, 7.87.

3,4-Dihydro-1H-2-benzothiopyran-4-carbonitrile (2c): 7c (1.48 g, 8.5 mmol) was dissolved in ethanol (100 ml). Under stirring $NaBH_4$ (1.62 g, 42,7 mmol) was added over a period of 15 min, subsequently the mixture was heated for 1.5 h at reflux temperature. After extraction (ether), drying ($MgSO_4$), evaporation and Kugelrohr distillation 1.32 g (88%) of **2c** were obtained as pale-yellow oil, bp (Kugelrohr) 80°C (0.02 mm Hg); DC: Rf = 0.5 (PE/EA=4:1); ^{1}H-nmr ($CDCl_3$): δ 7.47-7.00 (m,

4H), 4.10 (dd, J_{AX} = 4.8 Hz, J_{BX} = 6.6 Hz, 1H), 3.77 (s, 2H), 3.19 (dd, J_{AB} = 13.1 Hz, J_{AX} = 4.8 Hz, 1H), 3.11 (dd, J_{AB} = 13.1 Hz, J_{BX} = 6.6 Hz, 1H), ^{13}C-nmr ($CDCl_3$): δ 138.8 (s), 132.9 (s), 128.4 (d), 128.0 (d), 127.4 (d), 126.7 (d), 119.1 (s), 31.1 (t), 28.4 (s, t); Anal. Calcd for $C_{10}H_9NS$: C, 68.54; H, 5.18; N, 7.99. Found: C, 68.25; H, 4.92; N, 7.69.

General Procedure for the Syntheses of 3b-f and 3h (Method A): A solution of LDA (12 mmol) was prepared from 2.5 molar BuLi/*n*-hexane solution (5 ml, 12 mmol) in 40 ml of dry THF by addition of diisopropylamine (1.2g, 12 mmol) in dry THF (10 ml) at -40°C under N_2 atmosphere and stirring for 15 min. Subsequently the solution was cooled down to -80°C and the starting compound **2** (10 mmol), dissolved in 30 ml of dry THF, was added dropwise. After 1 h gaseous formaldehyde (20 mmol) - prepared by heating paraformaldehyde (0.6 g, 20 mmol) in a separated flask connected by a polyethylene-tube to the reaction vessel - was passed at -60°C through this solution, followed by stirring for additional 1 - 1.5 h (depending on the progress of the reaction determined from tlc-monitoring) at -40°C. Then most of the solvent was removed *in vacuo* and the mixture was hydrolyzed with 50 ml of 3N HCl (for **2c** and **2h** only 50 ml of H_2O had to be used). After extraction (ether, **2h**: methylene chloride), drying ($MgSO_4$) and evaporation **3b-g** and **3f** were obtained. The yields are given in *Table 1*, the physical properties are listed below.

***1-Hydroxymethyl-1,2,3,4-tetrahydro-1-naphthalinecarbonitrile* (3b):** yellow oil, bp (Kugelrohr) 110-120°C (0.01 mm Hg); Rf = 0.3 (PE/EA=3:1); ^{1}H-nmr ($CDCl_3$): δ 7.55-7.40 (m, 1H), 7.3-7.10 (m, 3H), 3.93 (d, 1H), 3.79 (d, J = 12.2 Hz, 1H), 2.90-2.75 (m, 2H), 2.50 (br s, 1H), 2.40-2.10 (m, 2H), 2.05-1.73 (m, 2H); ^{13}C-nmr ($CDCl_3$): δ 136.3 (s), 132.4 (s), 129.0 (d), 127.7 (d), 126.9 (d), 126.0 (d), 117.4 (s), 67.1 (t), 40.0 (s), 29.5 (t), 28.0 (t), 19.7 (t).

***4-Hydroxymethyl-3,4-dihydro-1H-2-benzothiopyran-4-carbonitrile* (3c):** After filtration over silica gel (eluent: PE/EA = 2:1) colourless crystals were obtained, mp 83-85°C; Rf = 0.7 (PE/EA=2:1); ^{1}H-nmr ($CDCl_3$): δ 7.60-7.00 (m, 4H), 4.21 (dd, J_{AB} = 11.3 Hz, J_{AX} = 7.9 Hz, 1H), 3.98 (dd, J_{AB} = 11.3 Hz, J_{BX} = 5.3 Hz, 1H), 3.66 (d, J_{CD} = 18.1 Hz, 1H), 3.44 (d, J_{EF} = 13.6 Hz, 1H), 3.42 (d, J_{CD} = 18.1 Hz, 1H), 3.32 (d, J_{EF} = 13.6 Hz, 1H), 2.24 (dd, J_{AX} = 7.9 Hz, J_{BX} = 5.3 Hz, 1H, OH); ^{13}C-nmr ($CDCl_3$): δ 133.1 (s), 130.7 (s), 129.5 (d), 129.0 (d), 128.1 (d), 127.4 (d), 122.2 (s), 66.7 (t), 43.5 (s), 31.2 (t), 30.1 (t); Anal. Calcd for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40; N, 6.82. Found: C, 64.13; H, 5.18; N, 6.61.

***α*-Hydroxymethyl-*α*-methylbenzenacetonitrile (3d):** After Kugelrohr distillation and filtration over silica gel (eluent: PE/EA = 3:1) a pale-yellow oil was obtained, bp (Kugelrohr) 80-110°C (0.1 mm Hg); Rf = 0.6 (PE/EA=3:1); ^{1}H-nmr ($CDCl_3$): δ 7.54-7.28 (m, 5H), 3.84 (d, J = 6.7 Hz, 2H), 2.25 (t, J = 6.7 Hz, 1H), 1.75 (s, 3H); ^{13}C-nmr ($CDCl_3$): δ 137.1 (s), 128.6 (2d), 127.9 (d), 125.7 (2xd), 122.4 (s), 69.1 (t), 44.6 (s), 22.2 (q).

***3-Hydroxy-2,2-dimethylpropanenitrile* (3e):** After Kugelrohr distillation a pale-yellow oil was obtained, bp (Kugelrohr) 80-110°C (0.1 mm Hg); ^{1}H-nmr ($CDCl_3$): δ 3.54 (s, 2H), 3.00 (br s, 1H), 1.37 (s, 6H); ^{13}C-nmr ($CDCl_3$): δ 124.0 (s), 67.8 (t), 34.5 (s), 21.7 (2q).

***1-Hydroxymethyl-1-cyclohexanecarbonitrile* (3f):** After Kugelrohr distillation a colourless oil was obtained, bp (Kugelrohr) 40-70°C (0.03 mm Hg); ^{1}H-nmr ($CDCl_3$): δ 3.61 (s, 2H), 2.60 (br s, 1H), 2.10-1.40 (m, 10H).

***4-Hydroxymethyl-1-methyl-4-piperidinecarbonitrile* (3h):** The crude product was triturated in diisopropyl ether/ether to give colourless crystals, mp 100-104°C; Rf = 0.5 (PE/EA/TEA= 15:4:1); ^{1}H-nmr ($CDCl_3$): δ 3.36 (s, 2H), 2.92-2.80 (m, 2H), 2.35-2.25 (m, 2H), 2.32 (s, 3H), 2.05-1.92 (m, 2H), 1.70-1.54 (m, 2H), 1.75 (br s, 1H); ^{13}C-nmr ($CDCl_3$): δ 122.0 (s), 67.5 (t), 51.7 (2t), 45.6 (q), 39.7 (s), 30.9 (2t).

General Procedure for the Syntheses of 3a and 3g (Method B): 2.0 ml of Triton B / MeOH solution were added slowly at ambient temperature and under N_2 atmosphere to a solution of **3** (10 mmol) and gaseous formaldehyde (15 mmol, preparation see method A) in dry toluene (20 ml). After stirring (**3a**: 3 days, **3g**: 2 h) the reaction mixture was worked up in analogy to method A. The yields of **3a** and **3g** are given in *Table 1*, the physical properties are listed below.

***4-Hydroxymethyl-4,5,6,7-tetrahydro-4-benzo[b]thiophenecarbonitrile* (3a):** After Kugelrohr distillation a colourless oil was obtained, bp (Kugelrohr) 120-130°C (0.03 mm Hg); Rf = 0.2 (PE/EA=3:1); ^{1}H-nmr ($CDCl_3$): δ 7.16 (d, J = 5.3 Hz, 1H), 7.07 (d, J = 5.3 Hz, 1H), 3.99 (d, J = 11.5 Hz, 1H), 3.83 (d, J = 11.5 Hz, 1H), 2.90-2.75 (m, 2H), 2.25-1.85 (m, 4H), 1.80 (br s, 1H); ^{13}C-nmr ($CDCl_3$): δ 139.2 (s), 129.5 (s), 125.2 (d), 123.3 (d), 122.2 (s), 67.1 (t), 40.9 (s), 29.8 (t), 24.3 (t), 19.7 (t).

***α-Hydroxymethyl-α-phenylbenzenacetonitrile* (3g):** after evaporation of the solvent a colourless oil was obtained; DC: Rf = 0.4 (PE/EA=4:1); ^{1}H-nmr ($CDCl_3$): δ 7.45-7.25 (m, 10H), 4.30 (s, 2H), 2.60 (br s, 1H).

General Tosylation-Procedure for the Syntheses of 4a-h: The starting compounds (5 mmol) were dissolved in 10 ml of dry pyridine (**4a-g**) or 30 ml of CH_2Cl_2 / 10 mmol of triethylamine (**4h**) and stirred at ambient temperature overnight. Work-up for **4a-g** was accomplished by addition of 3N HCl (50 ml) and extraction with CH_2Cl_2 or ether, drying ($MgSO_4$) and evaporation. The reaction mixture of **4h** was diluted with $CHCl_3$, washed with water, dried ($MgSO_4$) and evaporated. The yields for **4a-h** are given in *Table 1*, the physical properties are listed below.

***4-[[4-Methylphenylsulfonyl]oxy]methyl-4,5,6,7-tetrahydro-4-benzo[b]thiophenecarbonitrile* (4a):** Trituration with diisopropyl ether gave colourless crystals, mp 87-90°C; Rf = 0.4 (PE/EA=3:1); ^{1}H-nmr ($CDCl_3$): δ 7.85-7.75 (m, 2H), 7.40-7.30 (m, 2H), 7.05 (d, J = 5.5 Hz, 1H), 6.89 (d, J = 5.5 Hz, 1H), 4.23 (d, J = 10.0 Hz, 1H), 4.10 (d, J = 10.0 Hz, 1H), 2.90-2.70 (m, 2H), 2.46 (s, 3H), 2.28-1.80 (m, 4H); ^{13}C-nmr ($CDCl_3$): δ 145.2 (s), 139.9 (s), 132.0 (s), 129.9 (2xd), 127.7 (2xd), 127.5 (s), 124.8 (d), 123.7 (d), 20.1 (s), 71.0 (t), 38.2 (s), 29.8 (t), 24.1 (t), 21.5 (q), 19.2 (t).

***1-[[4-Methylphenylsulfonyl]oxy]methyl-1,2,3,4-tetrahydro-1-naphthalinecarbonitrile* (4b):** Trituration with diisopropyl ether gave colourless crystals, mp 79-80°C; Rf = 0.8 (PE/EA=3:1); ^{1}H-nmr ($CDCl_3$): δ 7.85-7.75 (m, 2H), 7.40-7.10 (m, 6H), 4.17 (s, 2H), 2.90-2.70 (m, 2H), 2.46 (s, 3H), 2.30-2.15 (m, 2H), 1.95-1.70 (m, 2H); ^{13}C-nmr ($CDCl_3$): δ 145.1 (s), 136.6 (s), 131.9 (s), 129.7 (2d), 129.2 (s), 128.6 (d), 127.8 (d), 127.6 (2d), 127.4 (d), 126.1 (d), 121.1 (s), 71.1 (t), 40.1 (s), 29.5 (t), 28.2 (t), 21.3 (q), 17.6 (t)

***4-[[4-Methylphenylsulfonyl]oxy]methyl-3,4-dihydro-1H-2-benzothiopyran-4-carbonitrile* (4c):** Trituration with diisopropyl ether gave colourless crystals, mp 94-95°C; Rf = 0.5 ($CHCl_3$); ^{1}H-nmr ($CDCl_3$): δ 7.70-7.60 (m, 2H), 7.45-7.23 (m, 6H), 4.56 (d, J = 10.6 Hz, 1H), 4.14 (d, J = 10.6 Hz, 1H), 3.96 (d, J = 16.6 Hz, 1H), 3.49 (d, J = 16.6 Hz, 1H), 3.25 (s, 2H), 2.45 (s, 3H); ^{13}C-nmr ($CDCl_3$):δ 145.2 (s), 133.1 (s), 131.8 (s), 129.8 (2 d, s), 129.6 (d), 129.3 (d), 128.8 (d), 128.0 (d), 127.7 (2 d), 120.0 (s), 70.1 (t), 40.7 (s), 31.3 (t), 29.8 (t), 21.2 (q).

***α-[[4-Methylphenylsulfonyl]oxy]methyl-α-methylbenzenacetonitrile* (4d):** Trituration with n-hexane / cyclohexane / diisopropyl ether (10:10:1) gave colourless crystals, mp 85-89°C; Rf = 0.7 (PE/EA=3:1); ^{1}H-nmr ($CDCl_3$): δ 7.80-7.60 (m, 2H), 7.40-7.30 (m, 7H), 4.15 (s, 2H), 2.44 (s, 3H), 1.76 (s, 3H); ^{13}C-nmr ($CDCl_3$): δ 145.1 (s), 135.2 (s), 131.8 (s), 129.7 (2d), 128.9 (2d), 128.5 (d), 127.6 (2d), 125.6 (2d), 120.3 (s), 73.1 (t), 42.0 (s), 22.7 (q), 21.3 (q).

***2,2-Dimethyl-3-[[4-methylphenylsulfonyl]oxy]propanenitrile* (4e):** Trituration with diisopropyl ether gave pale-yellow crystals, mp 80-82°C; Rf = 0.35 (PE/EA=3:1); ^{1}H-nmr ($CDCl_3$): δ 7.80-7.70 (m, 2H), 7.40-7.30 (m, 2H), 3.90 (s, 2H), 2.48 (s, 3H), 1.38 (s, 6H); ^{13}C-nmr ($CDCl_3$): δ 145.0 (s), 131.9 (s), 129.7 (2d), 127.5 (2d), 121.5 (s), 73.0 (t), 32.5 (s), 22.7 (2q), 21.1(q).

***1-[[4-Methylphenylsulfonyl]oxy]methyl-1-cyclohexanecarbonitrile* (4f):** Trituration with n-hexane / diisopropyl ether gave colourless crystals, mp 77-80°C; Rf = 0.8 (PE/EA=3:1); ^{1}H-nmr ($CDCl_3$): δ 7.87-7.72 (m, 2H), 7.42-7.29 (m, 2H), 3.95 (s, 2H), 2.47 (s, 3H)); 2.00-1.00 (m, 10H); ^{13}C-nmr ($CDCl_3$): δ 145.0 (s), 131.8 (s), 129.6 (2d) 127.6 (2d), 120.1 (s), 72.6 (t), 39.0 (s), 31.5 (2t), 24.5 (t), 21.8 (2t), 21.3 (q).

***α-[[4-Methylphenylsulfonyl]oxy]methyl-α-phenylbenzenacetonitrile* (4g):** Trituration with diisopropyl ether gave colourless crystals, mp 132-134°C; Rf = 0.8 (PE/EA=4:1); ^{1}H-nmr ($CDCl_3$): δ 7.75-7.65 (m, 2H), 7.40-7.25 (m, 12H), 4.61 (s, 2H), 2.45 (s, 3H); ^{13}C-nmr ($CDCl_3$): δ 145.1 (s), 135.6 (2s), 131.7 (s), 129.7 (2d), 128.8 (4d), 128.5 (2d), 127.6 (2d), 126.8 (4d), 119.5 (s), 70.8 (t), 51.5 (s), 21.3 (q).

***1-Methyl-4-[[4-methylphenylsulfonyl]oxy]methyl-4-piperidinecarbonitrile* (4h):** pale-yellowish crystals, mp 110-111°C; Rf = 0.2 (MeOH); ^{1}H-nmr ($CDCl_3$): δ 7.80-7.70 (m, 2H), 7.40-7.30 (m, 2H), 3.95 (s, 2H), 2.90-2.70 (m, 2H), 2.46 (s, 3H), 2.38-2.08 (m, 2H), 2.30 (s, 3H), 2.00-1.40 (m, 4H); ^{13}C-nmr ($CDCl_3$): δ 145.4 (s), 131.9 (s), 130.0 (2d), 128.0 (2d), 119.7 (s), 72.6 (t), 51.3 (2t), 45.8 (q), 37.3 (s), 31.3 (2t), 21.6 (q).

General Procedure for the Syntheses of Azetidines (5a-h): The starting tosylates **4** (5 mmol) were dissolved in 15 ml of dry THF or ether (see: *Table 2*) under N_2 atmosphere and 5 ml (5 mmol) of 1 molar-$LiAlH_4$/THF or ether solution was added. The reaction mixture was stirred at temperatures given in *Table 2* for different durations (see *Table 2*). Then crushed ice was added, the precipitated

inorganic salts were filtered off with suction and washed several times with ether. The obtained layer was concentrated *in vacuo* and extracted with 1N HCl. The acidic layer was washed with ether, made alkaline with 3N NaOH (pH=10) and extracted several times with methylene chloride. After drying ($MgSO_4$) and evaporation crude **5** was obtained. The products had to be purified individually as follows. The yields for **5a-h** are given in *Table 2*, the physical properties are listed below.

***6',7'-Dihydro-spiro[azetidine-3,4'(5'H)-benzo[b]thiophene]* (5a):** Kugelrohr distillation gave a colourless oil, bp 120-130°C (0.02 mm Hg); Rf = 0.15 (PE/EA/TEA=15:4:1); ^{1}H-nmr ($CDCl_3$): δ 7.28 (d, J = 5.0 Hz, 1H), 7.11 (d, J = 5.0 Hz, 1H), 3.88 (d, J = 8.4 Hz, 2H), 3.53 (d, J = 8.4 Hz. 2H), 2.85 (br s, 1H), 2.80-2.70 (m, 2H), 2.20-2.00 (m, 2H), 1.95-1.70 (m, 2H); ^{13}C-nmr ($CDCl_3$): δ 139.0 (s), 135.7 (s), 124.9 (d), 121.8 (d), 58.9 (2t), 39.6 (s), 34.4 (t), 24.5 (t), 20.4 (t).

***3',4'-Dihydro-spiro[azetidine-3,1'(2'H)-naphthaline]* (5b):** Kugelrohr distillation gave a colourless oil, bp 120-125°C (0.03 mm Hg); Rf = 0.5 (PE/EA/TEA=15:4:1); ^{1}H-nmr ($CDCl_3$): δ 7.90-7.78 (m, 1H), 7.36-7.00 (m, 3H), 3.88 (d, J = 7.0 Hz, 2H), 3.58 (d, J = 7.0 Hz, 2H), 3.10 (br s, 1H), 2.82-2.65 (m, 2H), 2.20-1.95 (m, 2H), 1.90-1.60 (m, 2H); ^{13}C-nmr ($CDCl_3$): δ 140.9 (s), 136.4 (s), 128.7 (d), 126.5 (d), 126.2 (d), 126.0 (d), 60.6 (2t), 41.5 (s), 36.2 (t), 30.0 (t), 19.9 (t).

***Spiro[azetidine-3,4'(3'H)-1H-2-benzothiopyran* (5c):** Kugelrohr distillation gave a colourless oil, bp 80-85°C (0.005 mm Hg); ^{1}H-nmr ($CDCl_3$): δ 7.78-7.74 (m, 1H), 7.37-7.02 (m, 3H), 3.97 (d, J = 8.6Hz, 2H), 3.68 (d, J = 8.6Hz, 2H), 3.70 (s, 2H), 3.20 (s, 2H), 2.35 (br s, 1H); ^{13}C-nmr ($CDCl_3$): δ 140.4 (s), 133.9 (s), 127.9 (d), 127.3 (d), 126.7 (d), 126.2 (d), 59.2 (2t), 42.4 (s), 37.7 (t), 30.6 (t).

***3-Methyl-3-phenylazetidine* (5d):** Kugelrohr distillation gave a colourless oil, bp 40-50°C (0.05 mm Hg); ^{1}H-nmr ($CDCl_3$): δ 7.77-7.04 (m, 5H), 4.02 (d, J = 10.0 Hz, 2H), 3.56 (d, J = 10.0, Hz 2H), 2.39 (br s, 1H), 1.66 (s, 3H); ^{13}C-nmr ($CDCl_3$): δ 148.5 (s), 128.4(d), 125.9 (d), 124.8 (d), 58.7 (t), 43.0 (s), 29.1 (q).

***3,3-Dimethylazetidine* (5e):** Due to its volatility the free base was only obtained as a mixture with THF (2:3 according to ^{1}H-nmr); ^{1}H-nmr ($CDCl_3$): δ 3.35 (s, 4H), 2.10 (br s, 1H), 1.23 (s, 6H); therefore **5e** was isolated as *N*-tosylate (3,3-Dimethyl-*N*-[4-methylphenylsulfonyl]azetidine) according to the general tosylation procedure given above yielding pale-yellowish crystals, mp 60-62.5°C; ^{1}H-nmr ($CDCl_3$): δ 7.75-7.65 (m, 2H), 7.40-7.30 (m, 2H), 3.43 (s, 4H), 2.43 (s, 3H), 1.05 (s, 6H); ^{13}C-nmr ($CDCl_3$): δ 143.8 (s), 131.6 (s), 129.5 (2d), 126.9 (2d), 62.5 (2t), 30.3 (s), 26.4 (2q), 21.4 (q).

***2-Azaspiro[3.5]nonane* (5f):** Kugelrohr distillation gave a colourless oil, bp 75-80°C (20 mm Hg); ^{1}H-nmr ($CDCl_3$): δ 3.32 (s, 4H), 3.10 (br s, 1H), 1.78-1.20 (m, 10H); ^{13}C-nmr ($CDCl_3$): δ 57.2 (2t), 39.2 (s), 36.3 (2t), 25.4 (t), 22.7 (2t).

***3,3-Diphenylazetidine* (5g):** Evaporation of the organic layer gave colourless crystals, mp 93-94°C; ^{1}H-nmr ($CDCl_3$): δ 7.36-7.20 (m, 10H), 4.26 (s, 4H), 2.20 (br s, 1H); ^{13}C-nmr ($CDCl_3$): δ 146.9 (2s), 128.5 (4d), 126.3 (4d), 126.26 (2d), 59.6 (2t), 50.8 (s).

***7-Methyl-2,7-diazaspiro[3.5]nonane* (5h):** Kugelrohr distillation gave a colourless oil, bp 80-85°C (0.04 mm Hg); ^{1}H-nmr ($CDCl_3$): δ 3.35 (s, 4H), 2.35 (br s, 1H), 2.35-2.20 (m, 4H), 2.21 (s, 3H), 1.83-1.70 (m, 4H); ^{13}C-nmr ($CDCl_3$): δ 57.1 (2t), 52.4 (2t), 46.2 (q), 37.6 (s), 35.9 (2t).

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