1-Aza[2.2]metacyclophane: A Ring Strained Secondary Amine

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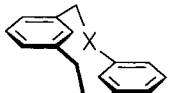
1-Aza[2.2]metacyclophane (**1**), the hitherto most strained cyclophane with a free NH group in the bridge, is synthesised for the first time with a remarkable yield in the last step by a combination of an intramolecular C–C-coupling reaction and removal of the *N*-TFA protecting group. The new amine **1** is obtained pure without chromatographic workup, simply by extraction with hydrochloric acid.

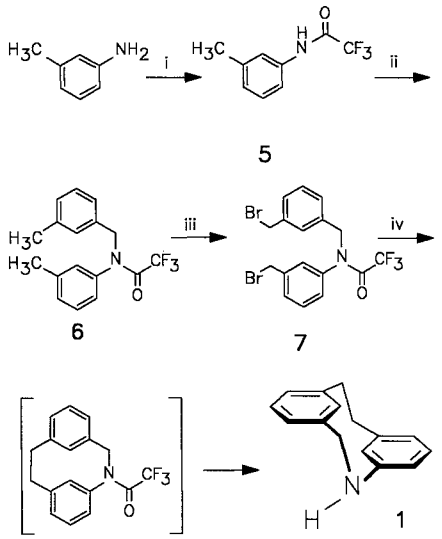
Strained amines are important synthetic targets in organic chemistry.[1] They are interesting to study for spectroscopic and steric problems, in particular due to nitrogen inversion in ring-strained molecules.[2] These properties are objects of intensive theoretical work, but often there is a lack of suitable model compounds to verify the results by comparison with experimental data. Obviously, one reason for this lies in the difficulty in obtaining strained secondary amines. Their preparation demands the introduction of *N*-protecting groups for activating the nitrogen atom and to avoid the formation of higher oligomers and alkylated products. Removal of these groups afterwards is hindered by the decreased reactivity of the bridging nitrogen unit. In particular sulfone containing protecting groups have proved to be resistant against any attempt of removal, as reported in the case of **4**.[3] Other *N*-protecting groups decrease the nucleophilic character of the nitrogen too strongly, so that the formation of small and other strained rings is not possible.



	X	R	Lit.
1	CH_2	H	
2	S	$COCF_3$	[4]
3	S	H	[4]
4	CH_2	Tos	[3]

Recently, we succeeded in the synthesis of 1-thia-10-aza[2.2]metacyclophane (**3**), which is the first [2.2]phane with a free NH-bridge.[4] For the synthesis of **3**, we introduced the trifluoroacetyl (TFA) group for activating the *N*-atom and to prevent oligomerisation. Using further special techniques (cesium effect, dilution principle),[5] we were able to prepare a TFA-protected aza[2.2]phane **2** instead of the hitherto exclusively used *N*-tosyl group. Hydrolysis under mild conditions yielded the free amine **3**. Our work dealing with the chiroptical properties of strained chiral aza[2.2]phanes is aimed at the synthesis of the sulfur-free parent aza[2.2]metacyclophane **1**. This contains no further hetero atom in its framework, and is more strained than **3**, due to the shorter C–C bond in **1** as compared to the C–S bridge in **3** (186 pm).

We report here the first synthesis of **1** using a new combination of the TFA-protecting method for preparing the C–N bridge first, with subsequent C–C bond formation via a phenyllithium coupling reaction. The phenyllithium coupling is well known in cyclophane synthesis,[6] yet it has not been used in the presence of a *N*-TFA substituent.



i: $(CF_3CO_2)_2O/Et_2O$, 0 °C (90%); ii: K_2CO_3/acetone/3-$BrC_6H_4CH_2Br$, reflux (86%); iii: NBS/AIBN/CCl_4, *hv*, reflux (26%); iv: PhLi (excess)/Et_2O, r.t. (58%).

We were successful in tailoring the reaction conditions in an appropriate way. This means that the ring-closure reaction has to run faster than the TFA-abstraction, because the resulting free amine would be able to react with the starting bromomethyl molecule **7**. Therefore **7** is added slowly to a large excess of phenyllithium in diethyl ether, which is an advantageous solvent for phenyllithium reactions. The TFA unit is also an appropriate choice for it increases the solubility of **7** in diethyl ether as compared to the tosyl group. Further, it is necessary to work at relatively high temperatures (r.t. or refluxing diethyl ether), so that the coupling reaction takes place fast enough. The achieved yield in the last step by the described coupling reaction (58%) is remarkably high compared to, e.g. the synthesis of 1-oxa[2.2]metacyclophane (yield: < 1%), the framework of which is similarly strained.[7]

The workup to isolate the amine can be simplified compared to other phenyllithium reactions, where numerous side products of phenyl addition interfere with the isolation of the desired target. We could isolate the amine **1** by extracting it as ammonium salt with dilute hydrochloric acid, leaving other lipophilic products in the organic phase. No further expensive chromatographic purification is needed. The free amine **1** is crystalline and suitable crystals were obtained for an X-ray investigation.[8]

In summary, this work provides an easy and efficient possibility to prepare strained secondary amines, which

are interesting starting materials for further synthetic applications. These special helical-chiral amines may also serve as chiral bases/auxiliaries in synthetic organic chemistry. Studies focusing on the steric and chiroptical properties of **1** as well as on the *N*-inversion behaviour will be the subject of future work.

Petroleum ether (PE) used had bp 40–60 °C. Satisfactory HRMS values were obtained for all new compounds: ± 0.0005 amu.

N-Trifluoroacetyl-3-methylaniline (5):
A solution of freshly distilled 3-methylaniline (10.7 g, 0.1 mol) in anhyd. Et_2O (150 mL) was stirred at 0 °C in an Ar atmosphere. A solution of $(CF_3CO_2)_2O$ (21.0 g, 13.9 mL, 0.1 mol) in anhyd Et_2O (40 mL) was added slowly. The mixture was allowed to warm up to r.t. and stirred for 2 h. 2 N HCl (100 mL) was added, and the aqueous layer extracted with Et_2O. The organic phase was dried (Na_2SO_4), the solvent removed and the product dried; yield: 18.3 g (90%); mp 59 °C. $R_f = 0.2$ (CH_2Cl_2/PE, 1:1).

^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 2.35$ (s, 3 H, CH_3), 7.0–7.4 (m, 4 H, ArH), 7.9 (br s, 1 H, NH).

^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 21.4$ (CH_3), 117.8, 121.3, 127.3, 129.2, 135.1, 139.5, 116.1 (q, $^1J_{C,F} = 284$ Hz, CF_3), 154.9 (q, $^2J_{C,F} = 28$ Hz, CO).

MS: *m/z* (%) = 203 (100, M^+), 134 (58, $M^+ - CF_3$), 106 (28, $M^+ - COCF_3$), 91 (74, $C_7H_7^+$).

N-(3-Methylbenzyl)-N-trifluoroacetyl-*m*-toluidine (6):
A stirred solution of 3-methylbenzyl bromide (13.9 g, 75 mmol) and K_2CO_3 (10.35 g, 75 mmol) in oxygen-free acetone (300 mL) was refluxed under anhydrous conditions. To this mixture was added a solution of **5** (15.3 g (75 mmol) in acetone (100 mL) over a period of 1 h. After the addition, the mixture was refluxed for further 6 h. The solvent was removed and the residue was dissolved in Et_2O. After filtration, the organic phase was washed with 1 N HCl and the HCl phase was extracted with Et_2O. The combined organic phases were dried (Na_2SO_4) and the solvent was removed to give the product as a colourless liquid; yield: 20 g (86%); $R_f = 0.5$ (CH_2Cl_2/PE, 1:3).

^{1}H NMR, (250 MHz, $CDCl_3$): $\delta = 2.32$ (s, 6 H, CH_3), 4.9 (s, 2 H, NCH_2), 6.8–7.3 (m, 8 H, ArH).

^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 21.06$ (CH_3), 21.25 (CH_3), 55.47 (NCH_2), 126.2, 127.7, 128.4, 128.5, 128.5, 128.8, 129.8, 129.9, 135.3, 138.3, 138.7, 139.2, 116.3 (q, $^1J_{C,F} = 281$ Hz, CF_3), 156.9 (q, $^2J_{C,F} = 38$ Hz, CO).

MS: *m/z* (%) = 307 (23, M^+), 105 (100, $C_8H_9^+$).

3-Bromomethyl-N-[3-(bromomethyl)benzyl]-N-trifluoroacetylaniline (7):
A solution of **5** (9.5 g, 31 mmol) in CCl_4 (500 mL) was refluxed and irradiated with a 500-W lamp under an Ar atmosphere. To this, a suspension of NBS (15.8 g, 88 mmol) and azoisobutyronitrile (AIBN) (15 mg) in CCl_4 (250 mL) was added in portions over a period of 1 h. After the addition, the mixture was refluxed and irradiated for further 6 h. The mixture was filtered, the filtrate washed with satd $NaHCO_3$ solution and subsequently with H_2O. After drying (Na_2SO_4), the solvent was removed and the residue was subjected to column chromatography (silica gel, 63–100 μm). The isolated product was recrystallised from EtOH; yield: 3.72 g (26%); mp 106 °C. $R_f = 0.7$ ($CHCl_3$/PE, 3:1).

^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 4.36$ (s, 2 H, CH_2), 4.43 (s, 2 H, CH_2), 4.85 (s, 2 H, NCH_2), 6.9–7.4 (m, 8 H, ArH).

^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 31.96$ (CH_2Br), 33.1 (CH_2Br), 55.12 (NCH_2), 125.5, 128.8, 129.1, 129.4, 129.5, 129.9, 130.1, 135.7, 136.0, 138.9, 139.5, 115.5 (q, $^1J_{C,F} = 285$ Hz, CF_3), 156.9 (q, $^2J_{C,F} = 39$ Hz, CO).

MS *m/z* (%) = 465 (10, M^+), 384/386 (40, $M^+ - Br$), 183/185 (95, C_8H_8Br), 104 (100, C_8H_8).

1-Aza[2.2]metacyclophane (1):
To a preheated and dried (Ar) 500 mL 2-necked flask was added a solution of PhLi [15 mL, 1.8 M in cyclohexane/Et_2O, 7:3, Aldrich, diluted by anhyd Et_2O (300 mL)]. Subsequently, a solution of the dibromide **7** (465 mg, 1 mmol) in anhyd Et_2O (50 mL) was added through a syringe/drain controlled by a pump over a period of 6 h at r.t. After the addition, the mixture was stirred for further 3 h. The solution was extracted several times with 2 N HCl. The combined HCl phases were neutralised, and extracted with Et_2O. The organic phase was dried (Na_2SO_4), the solvent removed, and the crude product was recrystallised from hexane; yield: 120 mg (58%); mp 72 °C; $R_f = 0.35$ ($CHCl_3$/MeOH/NH_4OH, 200:10:1).

^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 2.0–2.2$ (m, 2 H, CH_2), 2.8 (br s, 1 H, NH), 3.05–3.2 (m, 2 H, $2CH_2$), 3.4 (d, $J = 12.1$ Hz, 1 H, NCH_2), 4.0 (t, 1 H, $J = 2$ Hz, H_i), 4.3 (t, 1 H, $J = 2$ Hz, H_i), 4.3 (d, $J = 12.1$ Hz, 1 H, NCH_2), 6.9–7.4 (m, 6 H, ArH).

^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 41.36$ (CH_2), 41.4 (CH_2), 61.0 (NCH_2), 122.3, 124.2, 125.9, 127.1, 129.4, 130.1, 135.4, 136.6, 136.4, 139.1, 140.0, 145.9 (12 C_{arom}).

MS: *m/z* (%) = 209 (35, M^+), 208 (100, $M^+ - H$), 206 (40), 193 (18), 180 (10).

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(8) Supplementary material: The X-ray analysis indicates a centre of symmetry inside the molecule, due to a disorder of the NH unit. This cannot be distinguished by crystallography from the isoelectronic CH_2 group. The data are available on request from the authors.