

Synthesis of the novel amine (*R*,R*,R**)-tris-(α -methylbenzyl)amine. X-Ray crystal structures of racemic and enantiomerically pure forms

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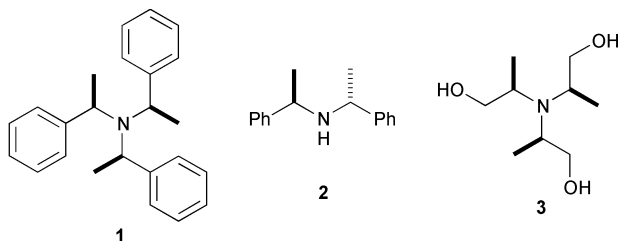
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Single diastereomers of tris(α -methylbenzyl)amine were efficiently synthesised in either racemic [(\pm)-**1**] or optically pure (**1**) form starting from α -methylbenzylamine. The X-ray crystal structures reveal virtually flat nitrogen centres.

Many chiral amines possess C_2 symmetry and several feature the α -methylbenzyl group.¹ The subject of C_3 symmetrical molecules has gained interest in recent years.² We report here the synthesis of the novel chiral amine **1**—an amine with three

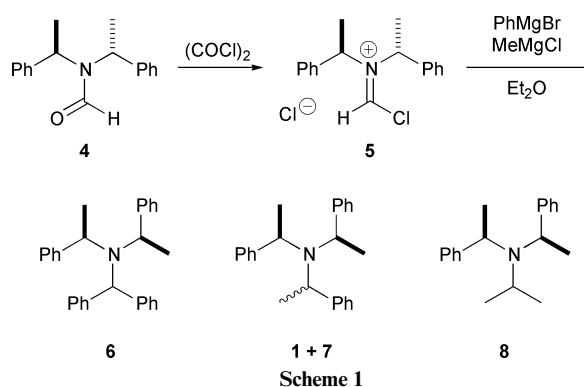


α -methylbenzyl groups that combines the features of steric hindrance, a synthetic challenge in itself,^{3,4} and C_3 symmetry. While several C_3 symmetrical amines are known,² there are only two C_3 symmetrical amine classes with chiral centres adjacent to the nitrogen atom; Van Vranken's ethanolamine (**3**)⁵ and Steglich's peptides.⁶ Amine **1** brings the total to three. It is made by an entirely different strategy and contains no functionality other than the amine itself.

The C_2 symmetrical amine **2** is well known and commercially available. In attempting to synthesise the C_3 symmetrical amine **1**, the challenge lies in introducing the third α -substituted benzyl group. Despite the apparently simple structure of **1**, we found it remarkably challenging to synthesise. We were unsuccessful with our initial synthetic strategies based around alkylation, reductive amination and carbenoid chemistry.

We synthesised C_2 symmetrical **2** from racemic α -methylbenzylamine by a variation of the method of Potapov.⁷ The hydrochloride of amine **2** was then transformed into formamide **4** in a 99% yield using triethyl orthoformate.

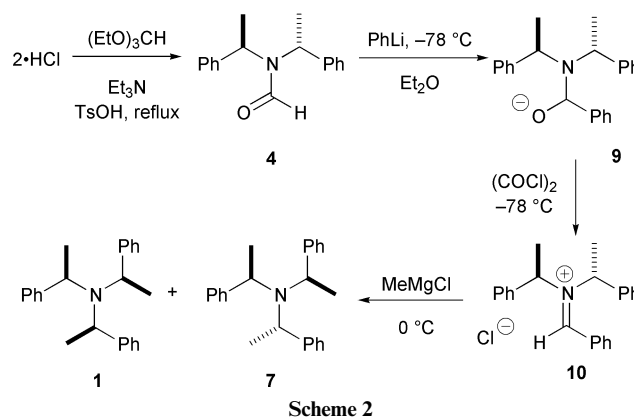
Although highly hindered amines, such as triisopropylamine, have been synthesised in good yield by exploiting the doubly electrophilic nature of chloroiminium chlorides,⁸ in our hands this strategy had limited success when it came to the synthesis of **1**. Chloroiminium chloride **5** was synthesised from formamide **4** using oxalyl chloride but attempts to introduce one phenyl group followed by a methyl group led to the introduction of either two phenyl groups (**6**) or, if the order of addition were changed, two methyl groups (**8**) (Scheme 1). We found that amine **1** could be synthesised from **5** only by the simultaneous addition, from separate syringes, of both PhMgBr and MeMgCl solutions. Not surprisingly, as well as diastereomer **7**, the amines **6** and **8** were also produced from the reaction



and the ratio of compounds **6**:(**1** + **7**):**8** was approximately 1:2:1.

We finally achieved selective construction of the third α -methylbenzyl group by starting with formamide **4** and separately introducing both the phenyl group and the methyl group as nucleophiles.

Phenyllithium was added to **4** at -78°C . Oxalyl chloride was added to the initial adduct (**9**) which was thus converted into what we presume is the iminium species **10**. The iminium chloride **10** reacted with MeMgCl at 0°C to give amine **1** and its diastereomer (**7**) in a total yield of 92% (Scheme 2). We were



pleased to find that the C_3 : C_1 diastereomeric ratio, at 4:1, was in our favour. We were not able to separate the diastereomers by column chromatography but trituration with pentane gave the C_3 symmetrical amine (\pm)-**1** in a 70% yield. We had suspected that amine **1** would be a highly crystalline compound and, compared to its diastereomer, it is indeed remarkably crystalline. Presumably this stems from the entropic advantage presented by the C_3 axis—any one molecule can necessarily pack with another in three degenerate ways. This is not the

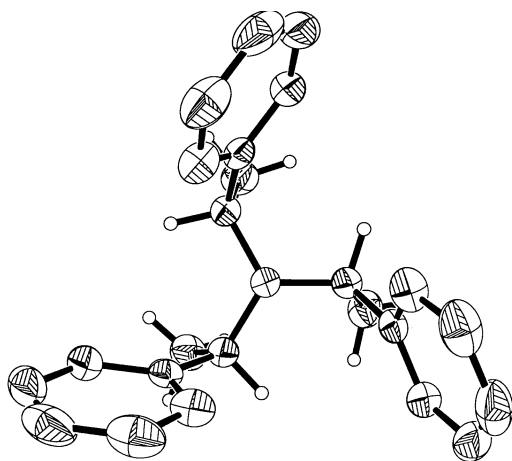


Fig. 1 Structure of (±)-1. View down C_3 axis, hydrogen atoms of phenyl groups omitted.

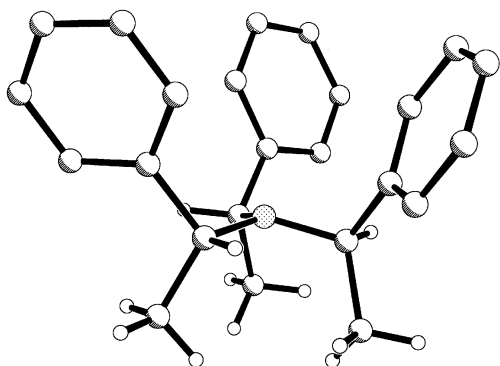


Fig. 2 Structure of (±)-1. View from side.

case with the diastereomer **7** which turns out to be an oil that is very soluble in pentane. Starting with optically pure α -methylbenzylamine, the same procedure was used to synthesise optically pure **1**.

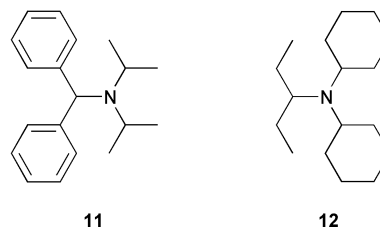
The crystal structure of racemic **1**[†] is of the rhombohedral (trigonal) $R\bar{3}$ space group. This space group has a C_3 axis of symmetry which passes through the nitrogen atom of amine **1**. In other words, amine **1** displays perfect crystallographic C_3 symmetry (Fig. 1). The unit cell contains both enantiomers of the amine. A given molecule of amine is related to its enantiomer through symmetry operations but the structure contains two crystallographically independent molecules of amine **1** (each of which has perfect crystallographic symmetry). Interestingly, the geometry at the nitrogen centre is virtually trigonal planar with a C–N–C bond angle of 117.2° (the other molecule in the asymmetric unit has a bond angle of 116.7°). The orientation of the three α -methylbenzyl groups is such that the nitrogen atom sits just above the plane defined by the three benzylic hydrogen atoms and the C–N–C–H dihedral angle is 168.4° (Fig. 2).

It is noteworthy that the C_3 symmetry of molecules rarely translates into the supramolecular world of their crystals. Indeed, the ‘crystal engineering’ of C_3 symmetrical molecules so that they form trigonal rather than hexagonal arrangements is a science in itself.^{9,10}

Naturally the unit cell of optically pure **1**[‡] contains only one enantiomer. Although the optically pure amine appears to also have C_3 symmetry this is not crystallographic. The crystal system is not trigonal but orthorhombic with a $P2_12_12_1$ space group—necessarily there is no C_3 axis of symmetry present. The molecular structures of the optically pure and of the racemic amines are extremely similar but with optically pure material the nitrogen atom is even closer to being trigonal

planar with C–N–C bond angles between 118.6° and 119.6° . The C–N–C–H dihedral angles are even closer to 180° and vary from 172.3° to 177.5° .

The pK_a of optically pure **1** was determined potentiometrically in H_2O –methanol and found to be 4.9. This is in line with other highly hindered amines. The pK_a values of **11** and **12**



have been determined (in 2-methoxyethanol) to be 4.0 and 5.0 respectively.⁸

In conclusion we have synthesised a highly hindered amine with a remarkable structure by a synthetic method not previously employed in an overall yield of 70% from the hydrochloride of **2**—a commercially available material. We have also demonstrated that a strategy which employs the use of oxalyl chloride *in between* the reaction of the two nucleophiles, facilitates control which is not available when oxalyl chloride is used at the outset. Whereas the latter strategy employs a chloroiminium chloride as a double electrophile, the former uses the formamide itself and an iminium chloride as the electrophiles. We imagine that this strategy will be of use to others for the construction of other highly hindered amines. The synthetic applications of amine **1** are being investigated in our laboratories.

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References and notes

[†] Crystal data for (±)-**1**—Single crystals were grown from petroleum ether (bp 40 – $60^\circ C$). $C_{24}H_{27}N$, $M = 329.47$, rhombohedral, $a = b = 11.522(2)$ Å, $c = 50.079(9)$ Å, $V = 5757.2(20)$ Å³, $T = 173(2)$ K, space group $R\bar{3}$, $Z = 12$, $\mu = 0.065$ mm⁻¹; 12373 reflections collected, 2942 [$R(\text{int}) = 0.0388$] independent reflections, $R_1 = 0.0443$ [$I > 2\sigma(I)$], $wR_2 = 0.1012$. CCDC reference number 207/494. See <http://www.rsc.org/suppdata/p1/b0/b007710k/> for crystallographic files in .cif format.

[‡] Crystal data for (+)-**1**—Single crystals of optically pure **1** were grown from ethanol. $C_{24}H_{27}N$, $M = 329.47$, orthorhombic, $a = 8.6255(3)$ Å, $b = 9.9353(4)$ Å, $c = 22.5592(7)$ Å, $V = 1933.25(12)$ Å³, $T = 160(2)$ K, space group $P2_12_12_1$, $Z = 4$, $\mu = 0.486$ mm⁻¹; 7381 reflections collected, 3266 [$R(\text{int}) = 0.0325$] independent reflections, $R_1 = 0.0311$ [$I > 2\sigma(I)$], $wR_2 = 0.0809$. The absolute stereochemistry could not be determined unambiguously but with a Flack parameter of $-0.1(6)$, the indicated structure is more likely and is in accord with the configuration of the starting material. CCDC reference number 207/494. See <http://www.rsc.org/suppdata/p1/b0/b007710k/> for crystallographic files in .cif format.

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