One-pot synthesis of some *N*-benzotriazol-1-ylmethyl-1,2,3,4-tetrahydroisoquinolines using benzotriazole-auxiliary

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Abstract

N-Benzotriazol-1-ylmethyl-1,2,3,4-tetrahydroisoquinolines are prepared at room temperature from the reaction between 1-hydroxymethylbenzotriazole (1), a 2-phenylethylamine (2a-e) and $AlCl_3$. This one-pot Friedel-Crafts reaction is a convenient improvement of the previously reported two-step procedure. The replacement of the benzotriazolyl moiety has often been demonstrated before; hence, the products of this reaction can be used as versatile, stable precursors for the preparation of various *N*-substituted 1,2,3,4-tetrahydroisoquinolines.

Keywords: One pot synthesis, benzotriazole, Friedel-Crafts reaction

Introduction

Isoquinoline alkaloids form one of the largest groups of alkaloids in the plant kingdom and have generated intense research over the decades due to their potent biological activities. With more than 50 different compounds found in nature, 1,2,3,4-tetrahydroisoquinolines constitute the largest group within the simple isoquinoline alkaloids. A wide variety of methods are available for their synthesis *in vitro* and the preparation of derivatives with electron-donating substituents on the aromatic moiety is easily achieved with classic methods such as the Pictet-Spengler or Bischler-Napieralski cyclisations. The preparation of 1,2,3,4-tetrahydroisoquinolines with electron-withdrawing substituents, however, is more challenging due to a decreased activity of the aromatic ring in an intramolecular electrophilic cyclisation. Stokker introduced an interesting approach, which is exclusively applicable to the preparation of 1,2,3,4-tetrahydroisoquinolines lacking electron-donating groups and therefore complementary to the Pictet-Spengler cyclisation. But there is still a need for more synthetic methods suitable for a wide variety of 1,2,3,4-tetrahydroisoquinolines independent from the nature of the substituents on the aromatic moiety.

The synthesis of some *N*-methyl-1,2,3,4-tetrahydroisoquinolines by Friedel-Crafts cyclisation using benzotriazole as auxiliary has recently been reported. This method is not only applicable to the preparation of 1,2,3,4-tetrahydroisoquinolines with activated aromatic systems, but also to

structures lacking electron-donating groups. In this note an improvement to the above procedure is described using one-pot conditions which involve the simultaneous reaction between 1-hydroxymethylbenzotriazole 1 and a phenylethylamine 2a-e facilitated by a Lewis acid. Reaction conditions are mild and yields generally high.

Results and Discussion

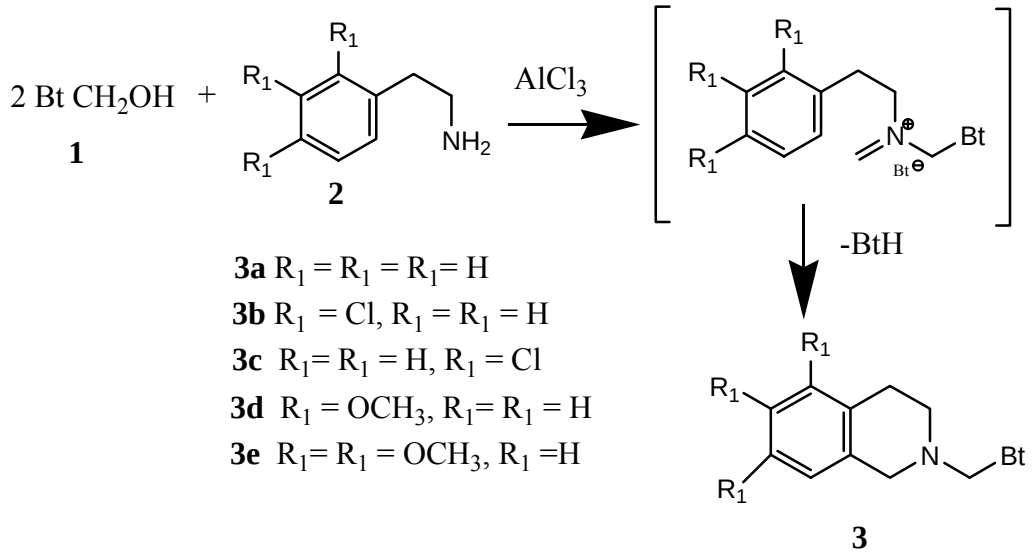
One-pot reactions have been reported before in benzotriazole chemistry. The simultaneous reaction between benzotriazole, various amines and formaldehyde or acetaldehyde in aqueous solution at 20 ^{o}C, for instance, yields 1-(α -aminoalkyl)-benzotriazoles.

In this case, 1-hydroxymethylbenzotriazole 1 (obtained from the well-known reaction between benzotriazole and formaldehyde) and a phenylethylamine 2a-e are reacted with anhydrous $AlCl_3$ in CH_2Cl_2 at room temperature for 30 hours. The reaction, which proceeds via an iminium ion (Scheme 1), yields crystalline *N*-benzotriazol-1-ylmethyl-1,2,3,4-tetrahydroisoquinolines 3a-e in very high quantities (Table 1).

As discussed previously in greater detail, the intramolecular cyclisation to compound 3e can lead to two isomers, the 6,7- as well as the 7,8-dimethoxy-substituted derivative. As anticipated, the reaction between 1-hydroxy-methylbenzotriazole 1 and 3,4-dimethoxyphenylethylamine 2e demonstrates a high level of regioselectivity and yields *N*-benzotriazol-1-ylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 3e as the main product.

The one-pot reaction also proceeds smoothly for *N*-benzotriazol-1-ylmethyl-5-chlorophenylethylamine 3c, which had unveiled some difficulties in a two-step procedure with respect to crystallisation and purified yield.

The remaining benzotriazolyl moiety in compounds 3a-e can be replaced by a variety of nucleophiles. Katritzky and co-workers have reported its replacement by Grignard reagents, alcohols and thiols. Under acidic conditions it can also be replaced by a variety of electron-rich heterocycles, such as 2-naphthol, indoles or pyrroles and also by methoxy-substituted benzenes. A further option is the reduction with NaBH4, which leads to the corresponding *N*-methyl-1,2,3,4-tetrahydroisoquinolines.



Scheme 1

Conclusions

In summary, the convenient one-pot reaction between 1-hydroxymethyl-benzotriazole 1, a phenylethylamine 2a-e and anhydrous $AlCl_3$ in CH_2Cl_2 at room temperature yields the corresponding crystalline *N*-benzotriazol-1-ylmethyl-1,2,3,4-tetrahydroisoquinoline 3a-e in good to excellent yields. This intra-molecular Friedel-Crafts cyclisation further improves the previously reported two-step reaction with respect to convenience and yields and allows the facile synthesis of compounds 3a-e as variable precursors for a variety of *N*-substituted 1,2,3,4-tetrahydroisoquinolines.

Table 1. *N*-Benzotriazol-1-ylmethylphenylethylamines 3a-e

R_1 3a H 3b Cl 3c H 3d OCH33e OCH_3	R_2 H H H OCH_3	R_3 H H Cl H H	Yield (%) 69 84 82 85 95	Mp/oC (EtOH) 155-157 146-148 144-145 128-130 137-140	δ[Bt-CH2-N] (ppm) 5.64 (s, 2H) 5.62 (s, 2H) 5.61 (s, 2H) 5.62 (s, 2H) 5.63 (s, 2H)	δ[Ar-CH2-N] (ppm) 3.86 (s, 2H) 3.80 (s, 2H) 3.81 (s, 2H) 3.82 (s, 2H) 3.77-3.84 (m, 8H)a

[a] Signal overlaps with those from -OCH3.

Experimental Section

General Procedures. All reagents used were AR grade. Melting points were determined on a Gallenkamp Melting Point Apparatus and are uncorrected. ^{1}H NMR spectra were recorded with a Varian Gemini 200 (200MHz) in deuteriochloroform ($CDCl_3$) using tetramethylsilane (TMS) as internal reference. Chemical shifts (δ) are reported in parts per million (ppm, δTMS = 0.00).

General procedure for the preparation of *N*-benzotriazol-1-ylmethyl-1,2,3,4-tetrahydroisoquinoline 3a

2-Phenylethylamine 2a (0.41 g, 3.4 mmol) was added to 1-hydroxymethyl-benzotriazole 1 (1.00 g, 6.7 mmol) with stirring. CH_2Cl_2 (30 mL) as well as anhydrous AlCl3 (1.79 g, 13.4 mmol) were added and the mixture stirred for 30 hours at room temperature with a drying tube (anhydrous $CaCl_2$) attached. The mixture was then poured on crushed ice (approx. 25 g), NaOH (2M, 30 mL) was added and the layers separated. The aqueous material was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic extracts were rewashed with NaOH (2M, 50 mL), dried with anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. Compound 3a crystallised quickly from an oily solution (0.62 g, 69%) and was recrystallised from EtOH.

***N*-Benzotriazol-1-ylmethyl-7-chloro-1,2,3,4-tetrahydroisoquinoline (3b).** 1Hydroxymethylbenzotriazole 1 (1.50 g, 10.1 mmol) was reacted with 4chlorophenylethylamine 2b (0.79 g, 5.1 mmol) and anhydrous $AlCl_3$ (2.72 g, 20.4 mmol). Compound 3b was obtained as white needles (1.28 g, 84%).

***N*-Benzotriazol-1-ylmethyl-5-chloro-1,2,3,4-tetrahydroisoquinoline (3c).** Compound 3c (1.24 g, 82%) was obtained as fine crystals from the reaction of 1hydroxymethylbenzotriazole 1 (1.52 g, 10.2 mmol) and 2-chloro-phenylethylamine 2c (0.79 g, 5.1 mmol) with anhydrous $AlCl_3$ (2.72 g, 20.4 mmol).

***N*-Benzotriazol-1-ylmethyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline (3d).** 1Hydroxymethylbenzotriazole 1 (1.02 g, 6.8 mmol) was reacted with 4methoxyphenylethylamine 2d (0.52 g, 3.4 mmol) and anhydrous $AlCl_3$ (1.84g, 13.8 mmol). Compound 3d (0.85 g, 85%) was obtained as white crystals.

***N*-Benzotriazol-1-ylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3e).** 1Hydroxymethylbenzotriazole 1 (1.52 g, 10.2 mmol) and 3,4-dimethoxy-phenylethylamine 2e (0.93 g, 5.1 mmol) were reacted with anhydrous $AlCl_3$ (2.74 g, 20.6 mmol) to yield compound 3e (1.56 g, 95%) as white needles.

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