Pergamon

Tetrahedron Letters 39 (1998) 3451–3454

TETRAHEDRON
LETTERS

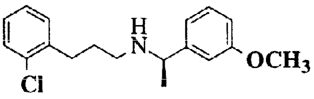
The Addition of Amines to Diisobutylaluminum-Imine Complexes. Preparation of NPS R-568 Hydrochloride

Robert M. Barmore, Sarah R. Logan and Bradford C. VanWagenen*
Department of Medicinal Chemistry, NPS Pharmaceuticals, Inc.
420 Chipeta Way, Salt Lake City, UT 84108

Received 15 December 1997; revised 4 March 1998; accepted 8 March 1998

Abstract: A facile procedure for the preparation of secondary and tertiary amines from nitriles has been developed. The addition of amines to diisobutylaluminum-imine complexes derived by treating nitriles with DIBAL-H was found to proceed in moderate to good yields and was used to prepare NPS R-568 (**1**) hydrochloride, a potent calcium receptor agonist.

NPS R-568 (**1**) hydrochloride represents a new class of arylalkylamine calcimimetics[1] that display agonist activity at the parathyroid cell calcium receptor and thereby inhibit parathyroid hormone secretion *in vivo*. NPS R-568 (**1**) hydrochloride is currently undergoing Phase II clinical trials for the treatment of primary and secondary hyperparathyroidism.

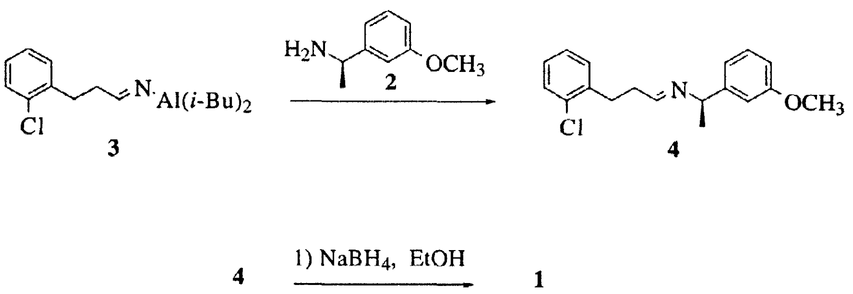


1

During the investigation of possible synthetic routes to **1**, we envisioned that (*R*)-1-(3-methoxyphenyl)ethylamine (**2**) might condense directly with the intermediate diisobutylaluminum-imine complex, **3**, to generate the imine, **4** (Scheme 1). Subsequent *in situ* reduction of **4** would afford the desired product, **1**.[2] Although a related condensation has been reported as a side reaction,[3] to our knowledge there have been no accounts which utilize this transformation as a part of a general amine synthesis. Recently, an intramolecular cyclization was used to prepare 3-methyl-5-hydroxy indoles,[4a] and a closely related reaction with cyanohydrins yielding amino alcohols was reported.[4b,4] Our first attempt at this "one-pot" procedure afforded **1** in low (~40 %) isolated yield, in part due to the formation of polymeric by-products. To optimize this procedure, we explored the effects of solvent, reaction time, and the number of amine equivalents used.

In our hands, the maximum yield for the synthesis of **1** was achieved as follows. DIBAL-H (1 equiv.) was added to a solution of 3-(2-chlorophenyl)propionitrile in CH_2Cl_2 (or toluene)[5] at -78 °C. After stirring for 1 h at room temperature, to ensure the formation of the intermediate diisobutylaluminum-imine complex, **3**, the reaction mixture was cooled to 0 °C, and treated with 2 equiv. of the amine **2**, for 3 h. The reaction mixture was treated with 1M ethanolic $NaBH_4$ at room temperature. Standard acid/base work-up followed by chromatography on silica gel, afforded **1**, in 82% yield.[6] Under these conditions, the use of less than 2 equivalents of amine **2** greatly affected the overall yield, with one equivalent of amine yielding only 55% of **1**.[2]

0040-4039/98/$19.00 © 1998 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(98)00603-0



Scheme 1. Addition of amines to diisobutylaluminum-imine complexes

To explore the generality of this procedure, we examined the addition of several amine nucleophiles to diisobutylaluminum-imine complexes. The results of this study are summarized in Table 1.[7] Entries 1-7 depict the consequences of adding primary amines. Reaction yields were found to be poor with relatively non-nucleophilic or hindered amines. Reaction with aniline, for example, afforded only modest amounts of product (42%). No coupling product was observed upon condensation of the indicated diisobutylaluminum-imine complex with *t*-butyl amine.

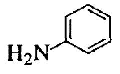
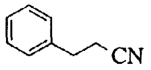
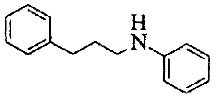
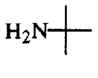
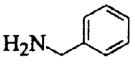
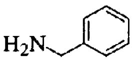
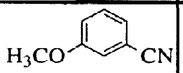
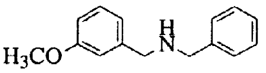
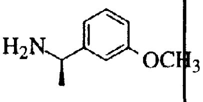
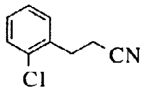
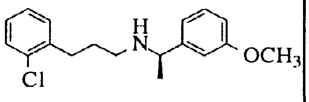
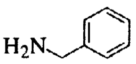
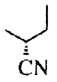
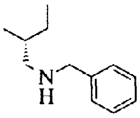
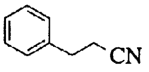
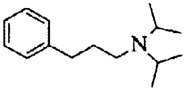
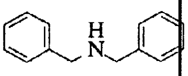
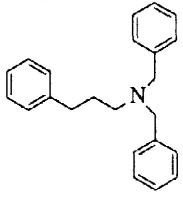
Entries 8 and 9 show that the addition of secondary amines to diisobutylaluminum-imine complexes is possible; however, the use of at least 3 equivalents of amine was required to achieve reasonable yields of tertiary amine products. Fewer than 3 equivalents of amine resulted in the formation of large amounts of unidentified side products after work-up.

Entry 7 demonstrates that deprotonation, with concomitant epimerization of a stereocenter α to the imine, is not a significant problem under these reaction conditions. Accordingly, treatment of (S)-(+)-2-methylbutyronitrile with DIBAL-H and benzylamine, followed by reductive work-up, gave the desired product in 86% yield with 95% ee.[8]

ACKNOWLEDGMENTS

We thank Tom Livinghouse, Frederick G. West, and Robert Smith for helpful discussions and assistance in the preparation of this manuscript.

Table 1. Addition of Amines to Diisobutylaluminum-Imine Complexes Derived By Adding DIBAL-H To Nitriles[a]

Entry	Amine	Nitrile	Product	Yield
1				42%
2		"	NR[b]	0%
3		"		88%
4		"		85%
5				82%
6				82%
7				86%
8				81%
9		"		36%

[a] using nitrile (1 equiv), DIBAL-H (1 equiv), and amine (2 equiv for primary amines and 3 equiv for secondary amines); [b] *t*-butylamine failed to add to the diisobutylaluminum-imine complex, workup afforded 3-phenylpropionaldehyde exclusively in 74% yield.

REFERENCES AND NOTES

1. (a) Steffey, M.E.; Fox, J.; Van Wagenen, B.C.; Delmar, E.G.; Balandrin, M.F.; Nemeth, E.F. *J. Bone Miner. Res.* **1993**, *8* (Suppl. 1), S175 (no. 236). (b) Nemeth, E.F.; Van Wagenen, B.C.; Balandrin, M.F. PCT Intl. Appl. No. WO 93 04,373 (*Chem. Abstr.* **1993**, *119*, P 63054s). (c) Van Wagenen, B.C.; Delmar, E.G.; Balandrin, M.F.; Steffey, M.E.; Nemeth, E.F. manuscript in preparation.
2. Van Wagenen, B.C.; D'Ambra, T.E. U.S. Patent 5,504,253, April 2, 1996.
3. Miller, A.E.G.; Biss, J.W.; Schwartzman, L.H. *J. Organic Chem.* **1959** *24*, 627-630.
4. (a) Marino, J.P.; Hurt, C.R. *Synth. Commun.* **1994**, *24*, 839-848.
(b) Zandbergen, P.; Brussee, J.; van der Gen, A.; Kruse, C.G. *Tetrahedron: Asymmetry* **1992**, *3*, 769-774. (c) Zandbergen, P.; van den Nieuwendijk, A.M.C.H.; Brussee, J.; van der Gen, A., Kruse, C.G. *Tetrahedron* **1992**, *48*, 3977-3982.
5. Toluene and dichloromethane were found to give optimal results, little or no product was observed using either THF or heptane.
6. Representative experimental: Preparation of (*R*)-N-(3-methoxy-1-phenylethyl)-3- (2-chlorophenyl)-1-propylamine (**1**). A stirred solution (at -78 °C) of 3-(2-chlorophenyl)propionitrile (0.83 g, 5.0 mmol) in dichloromethane (5.0 ml) was treated dropwise with diisobutylaluminum hydride (0.731 g, 5.05 mmol). The reaction was removed from the cold bath and allowed to stir at room temperature for 1 h. After this time, the reaction mixture was cooled to 0 °C and treated with (*R*)-α-methyl benzylamine (1.51 g, 10.0 mmol). After stirring for 3 h at 0°C, the reaction mixture was carefully treated with NaBH$_4$ (0.210 g, 5.5 mmol) in ethanol (5.5 ml) and then allowed to stir at room temperature for 1h. The reaction was quenched by the addition of dilute aqueous HCl (25 ml of 10% HCl) and then made basic by the addition of 1*N* NaOH. The organic layer was washed with water and dried over anhydrous MgSO$_4$. Filtration and concentration afforded the crude product. Flash chromatography (silica) using a gradient of CHCl$_3$ to CHCl$_3$/MeOH yielded the product, **1** (1.25 g, 82%), as a clear, colorless oil.
7. All of the products of these reactions were characterized by ^{1}H- and ^{13}C-NMR,and GC/MS. Each product has either successfully passed combustion analysis (Oneida Research Services, Inc.) or has been characterized by high-resolution mass spectrometry.
8. Enantiomeric purity was determined by chiral HPLC using a Chiralcel-OD HPLC column *vs.* a racemic standard prepared by the same method.