Pergamon

Tetrahedron Letters, Vol. 37, No. 7, pp. 945-948, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02335-6

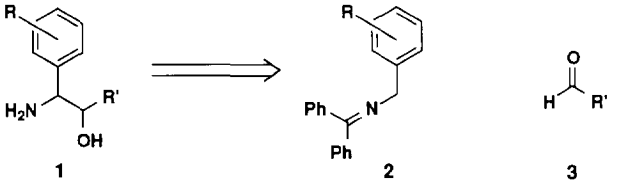
A Convenient Diastereoselective Synthesis of β-Aryl-β-Aminoalcohols

Charles Z. Ding
Bristol-Myers Squibb Pharmaceutical Research Institute, P. O. Box 4000, Princeton, NJ 08543-4000

Abstract: β-Aryl-β-aminoalcohols (**1**) were prepared from N-diphenylmethylene benzylamines (**2**) diastereoselectively in a one-pot procedure.

Vicinal aminoalcohols are an important class of compounds possessing pharmaceutical and biological properties.[1] Numerous synthetic methods exist for the preparation of β-aminoalcohols.[2] In an ongoing project in our laboratory, we were interested in the synthesis of β-aryl-β-aminoalcohols (**1**, Scheme 1). A convenient method for the generation of the β-aryl-β-aminoalcohol unit would involve simultaneous formation of the interconnecting carbon-carbon bond.[3] Such a method would allow the synthesis of diverse β-aryl-β-aminoalcohols (**1**) by combining differentially substituted benzylamines (**2**) and aldehydes (**3**). Realization of this strategy to generate β-aryl-β-aminoalcohol (**1**) in a diastereoselective manner is described in this communication.[4]

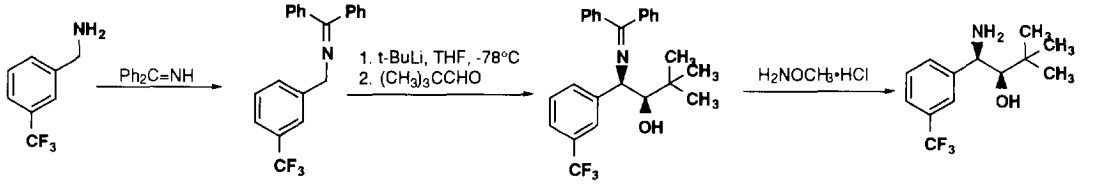
Scheme 1



By modifying O'Donnell's protocol,[5] 3-trifluoromethylbenzylamine (**4**) was allowed to react with benzophenone imine without solvent at 50 °C to give cleanly the benzophenone transfer product N-(diphenylmethylene)-3-trifluoromethylbenzylamine (**5**, Scheme 2). When the Schiff-base **5** was deprotonated by tert-butyl lithium in THF at -78 °C, a deep red solution resulted. Upon addition of trimethylacetaldehyde to the solution, the red color faded, resulting in the formation of coupling product **6**. Compound **6** was treated

with methoxylamine hydrochloride in methanol to yield a single aryl β-aminoalcohol **7** (by ^{1}H NMR analysis) in 44% yield.

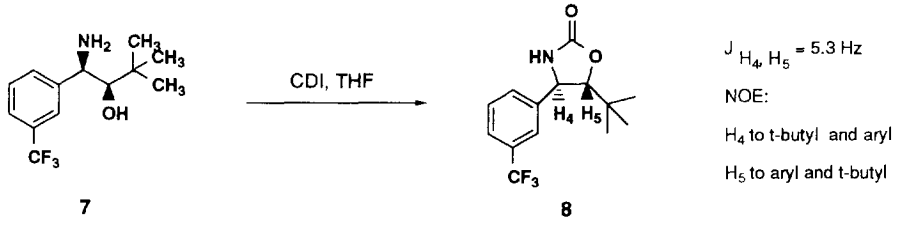
Scheme 2



4 **5** **6** **7**

The relative stereochemical assignment for the β-aryl-β-aminoalcohol **7** was derived from that of the oxazolidinone **8**, which was prepared by treatment of **7** with carbonyldiimidazole (Scheme 3). The relative stereochemistry of **8** was determined on the basis of the coupling constant ($J_{H4\text{-}H5}$), and NOE data. The coupling constant between H_4 and H_5 is 5.3 Hz indicating an *anti* arrangement.[6] Strong NOEs to the two substitutents (aryl and tert-butyl groups) were observed after irradiation of H_4, and no NOE was observed between H_4 and H_5. In addition, irradiation of H_5 resulted in enhancement of signals due to the aryl protons. These results support the *trans* arrangement between H_4 and H_5 protons. Thus, the coupling reaction gave exclusively the *syn* β-aryl-β-aminoalcohol (**7**).

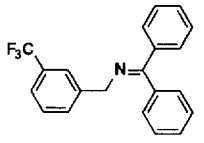
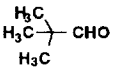
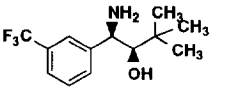
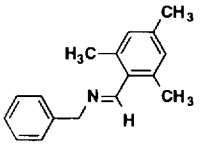
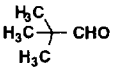
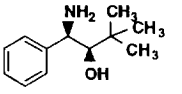
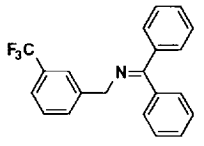
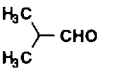
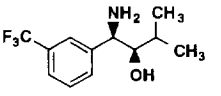
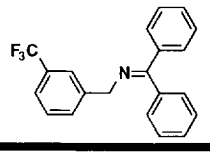
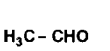
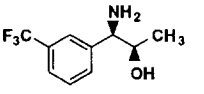
Scheme 3



7 **8**

The influence of the starting imines and aldehydes on the stereochemical outcome was briefly studied and the results are summarized in Table 1. When the mesitylimine (entry 2) was used as a Schiff base in place of the benzophenoneimine, good overall yield was obtained. However, the selectivity favoring the *syn* product dropped to 2:1. When isobutyraldehyde (entry 3) was used in place of trimethylacetaldehyde, exclusive formation of the *syn* product was observed. Even acetaldehyde (entry 4) gave preferentially *syn* product, albeit with lower selectivity (4:1). These results indicate that the bulky diphenylmethylene group of the imines (**2**) may be responsible for the observed *syn* selectivity, although the aldehydes also seem to play a role (entries 1, 3 vs. 4). The *syn* selectivity observed is in agreement with the observations made by Werf in his synthesis of α-amino-β-hydroxyacids from ethyl N-diphenylmethyleneglycinate.[7] The selectivity can be attributed to both chelation control and minimization of steric interactions in the transition state leading to the product **1**.[3b]

Table 1

entry	imine[a]	aldehyde	product[b]	syn/anti ratio[c]	yield[d]	mp (°C)
1				exclusive	44%	88-90
2				2:1	78%	79-81
3				exclusive	58%	96-97
4				4:1	55%	178-180[e]

Note: a. The imines were not isolated. b. The other diastereomers are not shown. c. The ratio was determined by NMR. d. The yields are isolated yields. e. HCl salt

In summary, N-diphenylmethylene benzylamines (substituted or otherwise) can be easily deprotonated and the resulting anions react with aldehydes to give preferentially the *syn* β-aryl-β-aminoalcohols. The present procedure represents a one-pot synthesis of β-aryl-β-aminoalcohols with high stereoselectivity.

A representative experimental procedure is provided (entry 3): A stirred mixture of 3-trifluoromethylbenzylamine (1.75 g, 10 mmol) and benzophenone imine (1.81 g, 10 mmol) was heated at 50 °C for 3 h. The resultant product was dissolved in anhydrous THF (50 mL), cooled to -78 °C under argon and *tert*-butyllithium (7 mL, 1.7 M in hexane, 11.9 mmol) was added *via* a syringe. The reaction mixture was allowed to stir for 15 min at - 78 °C and isobutyraldehyde (1.2 mL, 13.2 mmol) was added *via* a syringe. After stirring the resultant solution at -78 °C for 30 min and at 0 °C for 2 h, the reaction was quenched with acetic acid (1 mL). Solvent was removed *in vacuo*, and the residue was dissolved in methanol (20 mL). Methoxylamine

hydrochloride (1.5 g, 18 mmol) was added and the solution was stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the residue was partitioned between ethyl acetate and 10% HCl. The aqueous solution was separated, basified to pH 11 with 10 N NaOH solution, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo* to give a solid that was crystallized from ether-hexanes to give white crystals (1.4 g, 58%, m.p.: 96-97 °C). ^1H NMR (270 M Hz, $CDCl_3$) δ 1.02 (d, J = 7.0 Hz, 3 H), 1.05 (d, J = 7.0 Hz, 3 H), 1.60 (m, 1 H), 2.45 (bs, 3 H), 3.52 (dd, J = 4.5, 7.0 Hz, 1 H), 4.07 (d, J = 7.0 Hz, 1 H), 7.60 (m, 4 H). ^{13}C NMR (67.8 M Hz, $CDCl_3$) δ 16.64, 20.59, 30.20, 58.14, 79.97, 124.17, 124.23, 124.75, 124.80, 129.64, 130.76, 131.22, 145.05. MS (electrospray): 248 (M+H). Anal. calc'd for $C_{12}H_{16}NF_3O$: C, 58.29; H, 6.52; N, 5.66; F, 23.05. Found: C, 58.57; H, 6.51; N, 5.52; F, 23.36.

Acknowledgement: The author genuinely thanks Dr. Karnail S. Atwal for his unceasing encouragement and warm discussions. Thanks are also due to Ms. Yolanda Pan for her careful NMR experiments.

References:

1. a. Rich, D. H. *J. Med. Chem.* **1985**, *28*, 264;
   b. Kennedy, J. F.; White, C. A. *Bioactive Carbohydrates* Ellis Horwood: Chichester, England, 1983;
   c. Pettit, G. R.; Singh, S. B.; Hogan, F.; Lloyd-Williams, P.; Herald, D. L.; Burkett, D. D.; Clewow, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 5463
2. a. Kemp, J. E. G. In *Comprehensive Organic Synthesis* Trost, B. M.; Fleming, I.; Ley, S. V., Ed.; Pergamon Press: Oxford, 1991; Vol: 7, p 488.
   b. Mistsunobu, O. Ibid.; Vol: 6, p 88.
   c. Barrett, A. G. M.; Seefeld, M. A.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1053.
   d. Krepski, L. R.; Jensen, K. M.; Heilmann, S. M.; Rasmussen, J. K. *Synthesis* **1986**, 301.
   e. Jackson, W. R.; Jacobs, H. A.; Matthews, B. R.; Jayatilake, G. S. *Tetrahedron Lett.* **1990**, *31*, 1447.
3. a. Shono, T.; Kise, N.; Kunimi, N.; Nomura, R. *Chem. Lett.* **1991**, 2191.
   b. Kanazawa, A. M.; Correa, A.; Denis, J. -N.; Luche, M. -J.; Greene, A. E. *J. Org. Chem.* **1993**, *58*, 255.
4. a. Benzophenone Schiff base formation was used to protect and activate glycinamides:[7b] Kanemasa, S.; Mori, T.; Tatsukawa, A. *Tetrahedron Lett.* **1993**, *34*, 8293.
   b. N-Benzylidenebenzylamines were used for preparation of α-substituted benzylamines: Arrowsmith, J. E.; Cook, M. J.; Hardstone, D. J. *J. Chem. Soc., Perkin I* **1979**, 2364.
5. Preparation of benzophenone Schiff bases of amino acid derivatives, O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663.
6. Futagawa, S.; Inui, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3308.
7. a. Guanti, G.; Banfi, L.; Narisano, E.; Scolastico, C. *Tetrahedron* **1988**, *44*, 3671.
   b. Werf, A. W.; Kellogg, R. M.; Bolhuis, F. *J. Chem. Soc., Chem. Commun.* **1991**, 682.

(*Received in USA* 6 *November* 1995; *accepted* 4 *December* 1995)