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SUPERIOR CHIRAL RETENTION WITH LITHIUM AMIDE IN CYANOMETHYLATION OF N,N-DIBENZYL L-PHENYLALANINE BENZYL ESTER

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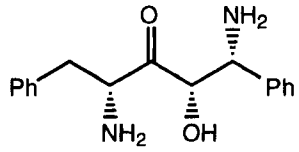
Abstract: Lithium amide is shown to give better retention of chirality over sodium amide in the nucleophilic addition of acetonitrile to N,N-dibenzyl L-phenylalanine benzyl ester. Solvent effect is obvious in the case of sodium amide.

In the synthesis of a protease inhibitor, Ritonavir(Norvir^{R}), for HIV, we needed to prepare a key "Core" intermediate, (2S,3S,5S)-2,5-diamino-3-hydroxy-1,6-diphenylhexane(1)[1] . One of the key steps in the



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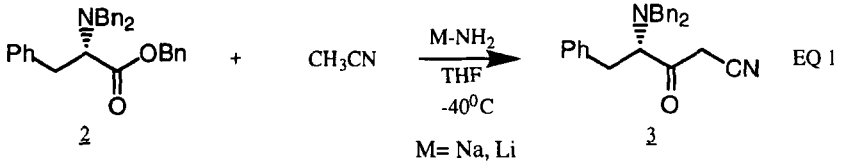
preparation of 1 was the cyanomethylation of N,N-dibenzyl L-phenylalanine benzyl ester(EQ 1). ß-Keto nitriles are important intermediates for the synthesis of a variety of synthetically useful and novel heterocyclic systems. Their synthesis and chemical reactivity have been reviewed[2].



Preparation of ß-keto nitriles such as 3 via nucleophilic displacement of cyanomethyl anion with an ester at elevated temperature had been shown to be an effective methodology[3]. Other examples[4] involving substrates containing a chiral center using cyanomethyl anion or its equivalent were carried out at very low temperature(-78 °C). Therefore, a practical procedure for the preparation of chirally pure ß-keto cyanide 3 is highly desirable.

In fact, addition of acetonitrile to benzyl ester 2 using potassium t-butoxide[5] initially had to be performed at -40 °C in tetrahydrofuran in order to achieve 96%ee. When potassium t-butoxide was substituted with sodium amide, similar ee could be obtained at somewhat higher temperature(-5 to -15 °C). However, during our scale-up studies with sodium amide, we also

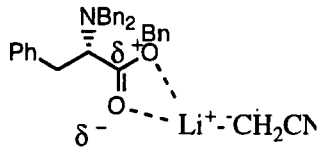
TABLE 1: Reaction of Acetonitrile with Benzyl Ester 2---Comparison of Sodium Amide vs. Lithium Amide

Entry	Base	Equivalent of Base	Solvent	Rxn. Temp, °C	%ee*	HPLC Purity %	%Yield
1	$NaNH_2$	3	THF	-15	98.0	99.7	79
2	$NaNH_2$	3	THF	0	79.2	92.4	37
3	$NaNH_2$	3	THF	25	70.5	91.5	66
4	$NaNH_2$	3	Toluene/THF (2:1 v/v)	-5	98.7	99.5	74
5	$NaNH_2$	3	Heptane/THF (2:1 v/v)	0	98.3	99.0	79
6	$NaNH_2$	3	MTBE	0	>99%	99.4	78
7	$LiNH_2$	2	THF	20	>99%	99.0	79
8	$LiNH_2$	3	Heptane/THF (2:1 v/v)	0	>99%	97.6	80
9	$LiNH_2$	3	Heptane/THF (2:1 v/v)	20	>99%	98.9	80
10	$LiNH_2$	3	MTBE	40	96.9	98.2	67

* Chiral assay was done using Chirapak AD Amylose tris(3,5-dimethylphenylcarbamate) column by Daicel Chemical Co. at 1.0 ml/ min and 205 nm. Eluent: 95:5 n-Hexane: Ethanol

noticed that the enantiomeric purity of 3 decreased with increasing scale and temperature. Fortunately, the reactivity of the sodium amide could be moderated by running the reaction in less polar solvent systems(see entry 4-6, Table 1), thereby, allowing the temperature to be increased to a more reasonable -5 °C. Unfortunately, sodium amide is pyrophoric, and can generate explosive mixture upon exposure to air and storage. Therefore, the handling and storage of sodium amide are serious issues for the manufacturing.

We now wish to report that replacement of sodium amide with non-pyrophoric lithium amide results in significant improvement in chiral retention at higher temperature in the same solvent systems. A literature and patent search found no precedence of such enhanced chiral retention by lithium amide. The results are summarized in Table 1. Table 1 shows that with sodium amide in THF, (entries 1-3), the enantiomeric excess is dramatically reduced from 98.0% to 70% when the reaction temperature is raised from -10 ^{0}C to 25 ^{0}C. The yields at higher temperatures also suffer. Whereas, with lithium amide, the reaction can be carried out at room temperature or even higher(entry 10) with better than 97%ee. This is probably due to the lower solubility of the lithium amide than sodium amide in these solvents. With lithium amide, deprotonation of acetonitrile is kinetically favored than the deprotonation of the α-proton of 2, thus resulting in better enantiomeric retention. It is also likely that there is a stronger chelation between lithium cation and carboxylic oxygen(see structure 4). Formation of the chelate 4 would increase the electrophilicity of the carboxylic carbon, and thus favor the nucleophilic addition of



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cyanomethyl anion to the carboxylic center than the deprotonation of the α-proton. This also explains the requirement of running the reaction at -40 ^{0}C when more THF soluble potassium t-butoxide is used. When sodium t-butoxide was used[5], a 78.2%ee was obtained in heptane/THF (2:1 v/v) at 0 ^{0}C. This was a slight improvement over potassium t-butoxide, but still much inferior to lithium amide. Interestingly, with lithium amide in MTBE, there was very little reaction at ambient temperature. Only at 40 ^{0}C would the reaction proceed at a reasonable rate. The solubility of sodium amide can similarly be reduced by running reactions in less polar solvents such as toluene/THF, heptane/THF or methyl t-butyl ether(entries 4-6, Table 1) to give improved enantiomeric purity of 3. Initial scaleup to 200 Kg with sodium amide in heptane/THF (2:1 v/v) reproduced our laboratory results.

In conclusion, lithium amide provides a safe and superior methodology for cyanomethylation of protected phenylalanine ester with no or very little racemization.

Experimental

General Procedure for the Reaction of N,N-Dibenzyl-L-phenylalanine Benzyl Ester with Lithium Amide.

A solution of N,N-dibenzyl-L-phenylalanine benzyl ester (49.7 g, 114 mmole) and acetonitrile (7.6 g, 171 mmole) in tetrahydrofuran (100 ml) was

added to a stirred slurry of lithium amide (5.6 g, 243 mmole) in tetrahydrofuran (100 ml) at 19 ^{0}C. There was no obvious exotherm during the addition. The colorless slurry was stirred at room temperature for 3 days, and quenched with a solution of citric acid (51.2 g) in water (153.6 g). The aqueous layer was separated, and the THF layer was washed with 70 ml of 15% aqueous NaCl. The organic layer was concentrated under vacuum to an oil. The oil was vigorously stirred with 135 ml of 70% ethanol/30% water until crystals formed. The slurry was cooled to 5 ^{0}C, the crystals were filtered, washed with cold 70% ethanol and dried under vacuum to give the desired keto-nitrile. Yield: 35.3 g(78.9%), %ee 99.4. MS: 369(M+H); H^1 NMR($CDCl_3$, δ) 7.35(m, 5H), 7.3(m, 10H), 7.15(m, 5H), 3.85(d, 1H), 3.82(d, 2H), 3.56(d, 2H), 3.51(dd, 1H), 3.2(dd, 1H), 3.05(d, 1H), 2.97(dd, 1H).

References

1. Elnagdi, M. H.; Elmoghayar, M. R. H.; Elgemeine, E. H.; *Synthesis*, **1984**, 1.

2. Stuk, T. L.; Haight, A. R.; Scarpetti, D.; Allen, M. S,; Menzia, J. A.; Robbins, T. A.; Parekh, S. I.; Langridge, D. C.; Tien, J. J.; Pariza, R. J.; Kerdesky, F. A.; *J. Org. Chem.* **1994**, *59*, 4040.

3. Levin, R.; Hauser, C. R.; *J. Am. Chem. Soc.*, **1946**, *68*, 760.

4. Brillon, D.; Sauve, G.; *J. Org. Chem.*; **1992**, *57*, 1838; Tomioka, K.; Koga, K.; *Tet. Lett.* **1984**, *25*(15) 1599.

5. Sou-Jen Chang, Abbott Laboratories, unpublished results.

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