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ASYMMETRIC DIALKYLATION OF α-CYANOACETIC ACID

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Summary: Formation of the quarternary asymmetric center by double alkylation of cyanoacetamide enolate bearing trans-2,5-bis(methoxymethoxymethyl)pyrrolidine moiety as a chiral auxiliary, was carried out with high diastereoselectivity.

Although chiral quarternary centers are often encountered in natural products, not many successful methods for the generation of such centers by asymmetric synthesis have so far been reported.[1] We have recently reported very efficient asymmetric monoalkylations of amide enolates with trans-2,5-disubstituted pyrrolidines as chiral auxiliaries.[2] However, the α-proton of the monoalkylated amides was difficultly abstracted because of its stereoelectronically disfavored orientation due to the steric congestion including the bulky chiral auxiliary, and further alkylation was not possible.[3] As one of the solutions of the problem, we examined the amide of cyanoacetic acid which bore an sp β-carbon atom of small steric requirement and thus found that the substrate could be dialkylated with high diastereoselectivity.

The first alkylation of (2R,5R)-N-cyanoacetyl-2,5-bis(methoxymethoxymethyl)pyrrolidine Li enolate proceeded smoothly giving a mixture of two diastereomers (**1**) with ratios of 1:1.6~1:2.1 in 94~96% yields. The low ratios are considered to be a reflexion of the poor (E)/(Z) ratio of the interemediary amide enolate due to a small difference in bulkiness between the cyano group and the hydrogen atom. The mixture of monoalkylated amides (**1**) thus obtained could be deprotonated by n-BuLi, as expected, and the second alkylation proceeded smoothly with high diastereomeric excesses of 80~90% (Table 1) in almost quantitative yields. Diastereomers of monobenzylated cyanoacetamide (entry 6) could be cleanly separated to each other, and either of the isomers underwent methylation giving the same major isomer with essentially the same diastereomeric ratio. Therefore, the stereochemistry of the major enolates formed by the second deprotonation is considered to be independent of the stereochemistry of monoalkylated amides. The above observation and the configuration of **3** determined on some examples indicate the predominant formation of the same (E)-enolate from both isomers of **1** and the subsequent approach of electrophiles to the re-re face of the enolate.

General experimental procedure: The starting amide prepared from α-cyanoacetyl chloride[4] and (2R,5R)-2,5-bis(methoxymethoxymethyl)pyrrolidine[2] in CH_2Cl_2 at rt (96% yield) was lithiated in THF with n-BuLi (1.63 mol dm^{-3}, 1.05 eq; -78 °C~-20 °C) and then treated with an alkyl halide (10 eq; -20 °C, 8 h). The usual workup including silica gel chromatography gave **1** as a mixture of two isomers (94~96% yield). **1** was lithiated, alkylated, and worked up in the same manner as above to afford the dialkylated product (**2**). **2** was then stirred with aqueous 6 mol dm^{-3} HCl for 12 h at rt, diluted with water, and then extracted with $CHCl_3$-EtOH (3:1). The evaporation residue of the extract was stirred with a solution of K_2CO_3 (1%) in MeOH for 12 h at rt. Extraction with CH_2Cl_2 and silica gel chromatography gave α,α-dialkylated cyanoacetic acid (**3**).

Scheme

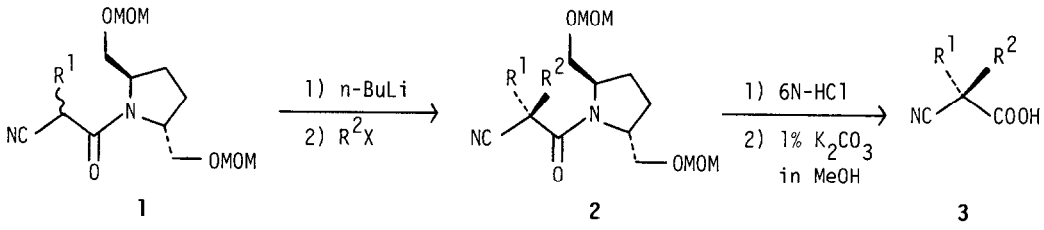

Table 1. Dialkylation of (2R,5R)-N-cyanoacetyl-2,5-bis(methoxymethoxymethyl)pyrrolidine[a)]

Entry	Dialkylation (2)[b)]				Hydrolysis (3)	
	R^1X	R^2X	Yield(%)[c)]	%de[d)]	Yield(%)	Configuration
1	CH_3I	C_2H_5I	96	90	75	R[e)]
2	CH_3I	$H_2C=CHCH_2Br$	96	90	83	R[f)]
3	CH_3I	$PhCH_2Br$	96	85	84	R[g)]
4	C_2H_5I	CH_3I	96	80	73	S[e)]
5	$H_2C=CHCH_2Br$	CH_3I	94	84	87	S[h)]
6	$PhCH_2Br$	CH_3I	94	84	92	S[g)]

a) All new compounds gave satisfactory elementary analyses and ^1H NMR data. b) A diastereomeric mixture of monoalkylated amides was used in the second alkylation without separation. c) Overall isolated yield. d) Determined by intensities of relevant ^1H NMR signals. e) Tentative assignment by analogy. f) The configuration of the dialkylated amide was correlated with that of another dialkylated amide ($R^1=CH_3$, $R^2=PhCH_2$; configuration, cf. reference g) by transforming them into the same (^1H NMR) N-(3-methoxycarbonyl-2-cyano-2-methylpropionyl)-2,5-bis(methoxycarbonyloxymethyl)pyrrolidine by successive oxidation ($RuCl_3$-$NaIO_4$) and esterification (CH_2N_2). g) Determined from the sign of optical rotation by comparison with the authentic data; S. Terashima, K.K.Lee, and S.Yamada, Chem. Pharm. Bull., **17**, 2533 (1969). h) Determined from the sign of optical rotation by comparison with that of the acid obtained in entry 2.

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References and Notes

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