

Conformational Preferences in Diastereomers. III. Addition Products from Unsaturated Nitriles

CHARLES A. KINGSBURY

Chemistry Department, University of Nebraska, Lincoln, Nebraska 68508

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The diastereomers resulting from alkylmagnesium halide addition to α -phenylcinnamionitrile were studied. Increasing the steric requirements of the alkyl groups results in a trend toward low vicinal coupling constants in the most stable, crystalline diastereomer, which is assigned to the *erythro* configuration. Conversely, the *threo* diastereomer moves toward high J values. The effect of various quenching media on the intermediate carbanion is interpreted in terms of an S_{Ei} mechanism.

From earlier work¹⁻⁵ on conformational preferences in diastereomers, a fairly clear picture is beginning to emerge concerning the most favored disposition of various groups. This can be seen with the aid of Figure 1, in which L, M, and S refer to the size of the groups. The designation *erythro-s* indicates the assignment of configuration is based on size.⁶

When there is a substantial difference in the steric requirements of the large and medium groups (L and M) it appears the L groups will prefer a *trans* orientation. In the other diastereomer, if the L groups are *trans*, the S groups likewise must be *trans*. If S is hydrogen the nuclear magnetic resonance vicinal coupling constant J will be large, ca. 10–12 cps. In the diastereomer the S groups will be *gauche* and J will be small, ca. 1–3 cps.

Noteworthy exceptions to this generalization exist. When both L and M groups are similar in steric requirements, both diastereomers frequently have quite large coupling constants.⁷ In either case, if the hydrogens are *trans*, the total number of *gauche* interactions between sizeable groups is decreased compared to a rotomer involving *gauche* hydrogens.

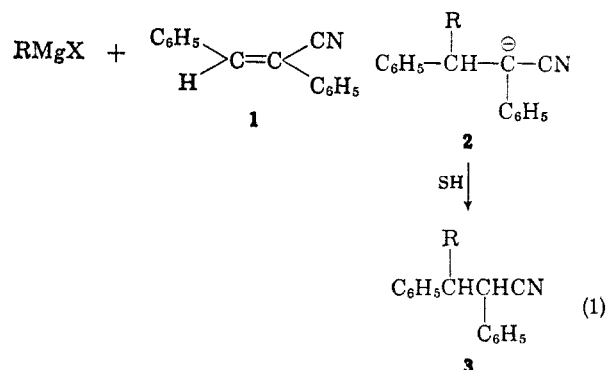
In other cases, where only one group in the molecule can be considered large, other rotomers than the ones shown in Figure 1 have significant weight. Close to the "averaged" coupling constant, $J = 5-8$ cps, is frequently observed.^{2,7}

In still other cases the interactions of groups may be attractive rather than repulsive, e.g., where intramolecular hydrogen bonding is important.⁸⁻¹¹ In these cases the *erythro-s* J value may be lower than the *threo-s* value.

Diastereomers containing the *t*-butyl group frequently represent unexplained anomalies characterized by low coupling constants.^{7,12,13}

The present study concerns a series of diastereomers

derived from Grignard addition to unsaturated nitriles (eq 1), a reaction first observed by Kohler and Reimer.^{14,15}



It was the purpose of this study to (1) observe the vicinal coupling constants of the two diastereomeric products (**3**) and to assign configurations to the two isomers, (2) observe the relative stabilities of the two isomers, and (3) observe the ratios of the isomers of **3** as a function of quenching of the intermediate **2** by various proton-donating systems.

Results and Discussion

Conformational Preferences and Configurations.—

It had been hoped that Grignard addition to a variety of substrates would be possible. Unfortunately attempted addition to an α -methylcinnamionitrile was not successful, as was attempted addition to the β -naphthyl and β -*o*-chlorophenyl analogs of **1**. Addition of alkyllithiums resulted in a plethora of products, very little of which was the desired product **3**.

Addition of alkylmagnesium halides, however, was a smooth reaction providing an excess of the Grignard reagent was used. The intermediates **2** were usually red in color and were quenched to form **3** cleanly except in the case of $\text{R} = \text{CH}_3$ when some side products were evident. The nmr resonance absorptions of the two diastereomers of formula **3** were well separated and the coupling constants could be accurately determined from the spectrum of the mixed diastereomers (Figure 2). These data are listed in Table I. In our hands only one of the diastereomers was high melting and easily obtained pure. The second diastereomer was usually an oil and it was very difficult to separate this material completely from the high-melting product and traces of **1**. Chroma-

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(5) C. A. Kingsbury and W. Thornton, *J. Amer. Chem. Soc.*, **88**, 3159 (1966).

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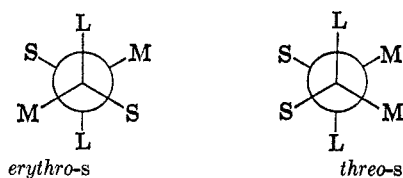


Figure 1.

TABLE I
VICINAL COUPLING CONSTANTS^a OF THE GRIGNARD
ADDITION PRODUCTS 3

R	erythro ^{c,d}			threo ^c		
	δ_A , ppm	δ_B	J_{AB} , cps	δ_A	δ_B	J_{AB}
CH ₃ ^b	3.23	3.94	7.2	3.19	3.94	6.8
C ₂ H ₅	2.84	3.98	6.4	Ca. 2.8	3.86	7.1
<i>i</i> -C ₃ H ₇	Ca. 2.4	4.29	4.8 ^h	2.95	4.17	8.4 ⁱ
<i>t</i> -C ₄ H ₉	2.61	4.36	3.7	2.99	4.03	10.2
S-C ₆ H ₅ ^g	4.12	4.28	5.5	4.15	4.45	7.1
C ₆ H ₁₁ ^e	2.51	4.31	5.3 ^f	2.97	4.22	8.3 ^f

^a Spectra taken on a Varian A-60 instrument. Concentration was 10% by wt/v of CCl₄ except as indicated. Coupling constants were determined from expanded spectra. ^b Concentration 10% in CDCl₃. ^c For justification of this assignment, see text. ^d High-melting isomer, physical constants are given in the Experimental Section. ^e Cyclohexyl. ^f These J values varied ± 0.2 cps over a fourfold change in concentration. ^g Anionic addition product rather than Grignard product. ^h This value should be regarded as approximate; some virtual coupling was evident. ⁱ $J_{\text{isopropyl-A}} = 6.0$ cps.

tography on silica gel afforded considerable separation, however, the spectrum of all fractions still indicated contamination of the oil by the high-melting product. Chromatography on alumina resulted in equilibration giving a predominance of the high-melting product.

As the data in Table I show, for R = CH₃, there is little difference in the J values for the two products. Both values are close to the "averaged" coupling constant indicative of little or no conformational preferences. This represents one more illustration of the fact that phenyl is little different from methyl in effective size. As the bulk of R increases the coupling constants of the high-melting isomer move monotonically toward low values. These values are taken as indicative of a growing predominance of a rotomer with *gauche* protons.

On the other hand, the J values of the other isomer move toward high values indicative of a predominant rotomer with *trans* protons. In the case of R = *t*-butyl near conformational purity is evident.

The diastereomers of this study were comparatively well behaved in that there was no discontinuity in J in moving from R = isopropyl to R = *t*-butyl as was observed in other studies.^{7,13}

With the above data in hand, a tentative assignment of configuration may be made. Here it is convenient to move to the alternate definition of configuration to avoid confusion when groups are of similar size. The *erythro* isomer is taken as the material in which like groups can be eclipsed.^{1,3,8} The assignments of configuration are illustrated for R = *t*-butyl in Figure 3.

If one assumes the most stable rotomer has the largest groups *trans*, the low coupling constant product (*gauche* protons), which is also the crystalline product,

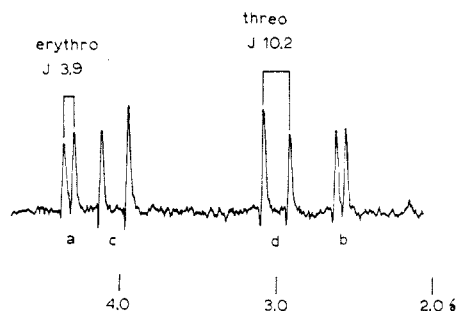


Figure 2.—Partial nmr spectrum of mixed diastereomers of 3, R = *t*-C₄H₉, resulting from NH₄Cl-ice quench of carbanion 2. An internal standard, tetramethylsilane, was taken as 0 ppm. The resonance absorptions a, b, c, and d are assigned as shown in Figure 3.

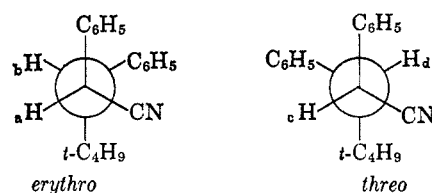


Figure 3.

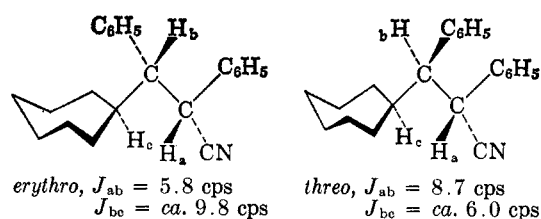


Figure 4.

is the *erythro* diastereomer. The other crystalline products (R = CH₃, etc.) by analogy are also assigned the *erythro* configuration.

It is interesting to compare the R = isopropyl and R = cyclohexyl cases. Previous it had been shown^{4,7} that, if J_{ab} is large, J_{bc} would be small and *vice versa*. The cyclohexyl as well as the isopropyl compounds exhibit the same phenomenon. This alternation of J values can be explained with the aid of extended conformational diagrams such as in Figure 4. These compounds are less conformationally pure than other examples and only one rotomer of the *erythro* and *threo* is shown. By arranging protons a and b *gauche* and b and c *trans* (or *vice versa*) 1,3 interactions are minimized. In each case H_c is opposite the CN and H_a opposed to one arm of the cyclohexyl ring. If J_{ab} and J_{bc} were both large or both small the conformation would involve a severe 1,3 interaction between sizeable groups.

Equilibrium Experiments.—The base-catalyzed equilibration results for several diastereomers in methanol are listed in Table II.

TABLE II
EQUILIBRATION EXPERIMENTS OF 3^a

% <i>erythro</i> of an <i>erythro</i> - <i>threo</i> mixture (temp, °C)			
R = CH ₃	R = <i>i</i> -C ₃ H ₇	R = C ₆ H ₁₁	R = <i>t</i> -C ₄ H ₉
55 (27)	77 (25)	72 (27)	82 (24)

^a Solution of ca. 200 mg of substrate in 20 ml of 0.06 N NaOCH₃-CH₃OH. ^b These results are considered good to $\pm 5\%$.

It is evident from Table II that the *t*-butyl compound not only exhibits the strongest conformational preferences but also the greatest difference in stability between the two isomers. This difference is perhaps smaller than anticipated considering the relative sizes of the alkyl groups.

For the R = *t*-butyl case, where the two diastereomers are close to conformational purity, it is instructive to count up the *gauche* interactions in each diastereomer. Assuming the dihedral angles are close to 60°, equivalent *gauche* interactions in the *erythro* and *threo* isomers may be cancelled. The stability of the *erythro* then is associated with a lower energy of interaction of *gauche* C₆H₅-CN and H-H groups over *gauche* C₆H₅-H and CN-H groups in the *threo* isomer. On the basis of steric hindrance this seems unlikely, since in the *threo* both interactions involve hydrogens. However, it is possible that the C₆H₅-CN interaction in the *erythro* is attractive rather than repulsive, since both groups should be "soft" according to the Chatt-Pearson point of view,^{16a} and polarizability effects may be significant.^{16b}

More likely dihedral angles are not exactly 60°. A slight clockwise rotation of the *t*-butyl, *et al.*, groups is possible (Figure 3). In the *erythro* isomer this rotation does appear to relieve steric interference (from Stuart-Breigleb models). However, the C₆H₅-C₆H₅ interaction is worsened in the *threo* case. This sort of rotation may be denied the *threo* isomer which may account in part for its instability.

Carbanion Quenching Experiments.—Various *erythro*-*threo* ratios resulted depending on the proton-donating medium used to destroy the carbanion **2**. The media used were NH₄Cl over ice, ethanol, acetic acid, and anhydrous HCl in ether. The data are recorded in Table III. It is seen that the more stable *erythro* isomer is usually the predominant product. As the steric requirements of the R group increase, the trend is toward increasing amounts of the *threo* isomer.

TABLE III

threo-*erythro* RATIOS^d IN **3** FROM VARIOUS QUENCHING MEDIA

Medium	R			
	CH ₃	<i>i</i> -C ₄ H ₇	C ₆ H ₁₁	<i>t</i> -C ₄ H ₉
NH ₄ Cl-ice	0.6 ^c	0.68	0.88	1.14
C ₂ H ₅ OH	0.5	0.62	0.80	0.92
HOAc-(C ₂ H ₅) ₂ O ^a	0.5	0.50	0.70	0.52
HCl-(C ₂ H ₅) ₂ O ^b	0.3	0.39	0.72	0.53

^a The mixture was 10 ml of acetic acid in 20 ml of anhydrous ether. ^b Anhydrous HCl was passed into 20 ml of anhydrous ether for *ca.* 10 min. ^c The ratio for HCl-ice was similar. ^d These values are considered good to ±6%, except R = CH₃ (±10%).

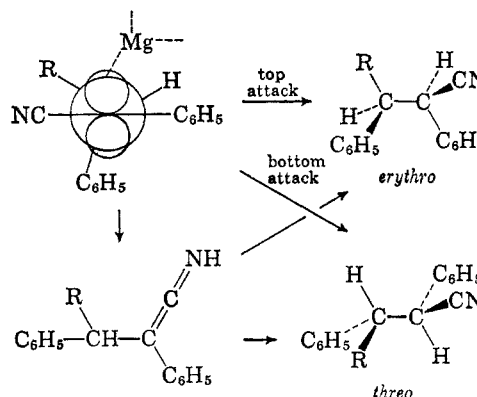
The carbanionic center may be either sp² or sp³ hybridized. However, since the negative charge may be delocalized into both cyano and phenyl groups a planar carbanionic center seems more likely.^{17,18} However, the following discussion would not be materially changed if an sp³ center were assumed.

(16) (a) R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, **89**, 1827 (1967); (b) L. I. Peterson, *ibid.*, **89**, 2680 (1967).

(17) (a) E. Grovenstein, Jr., and G. Wentworth, *ibid.*, **85**, 3305 (1963); (b) D. J. Cram, R. Rickborn, and W. Neilsen, *ibid.*, **82**, 6416 (1960).

(18) See, however, M. Witanowski and J. D. Roberts, *ibid.*, **88**, 737 (1966).

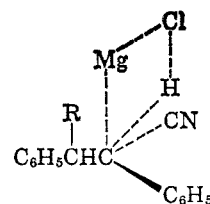
Ignoring for the moment the effect of the magnesium cation, a rationalization for the effect of the R group may be given with the aid of the theoretical model developed by Zimmerman and Chang⁶ (Figure 4).



This model seems quite good for R = isopropyl, cyclohexyl, and *t*-butyl. With increasing size of the R group, attack by the proton donor from the top to give *erythro* product becomes increasingly difficult.^{19,20} In the extreme case the R = *t*-butyl group shields the top of the molecule to the extent that bottom attack predominates in one case even though this involves momentary eclipsing of groups. Another possible route is initial protonation on nitrogen followed by rearrangement.²¹ With exceptions Zimmerman and coworkers have shown such proton transfers often give predominately the least stable isomer,^{19,20} which is not observed in this study.

It is somewhat more difficult to rationalize the effects of the various proton donors. Unlike the cases observed by Russell,²¹ the acidic media give a more stereoselective product mixture in which the more stable isomer predominates.

It is thought that the influence of the cation is greater in the fairly low dielectric constant ethereal solvents than in the hydroxylic solvents. Extensive ion aggregation appears likely. A four-center mechanism is attractive with coordination between the chloride or acetate and the magnesium. This type reaction bears some similarity to the reactions at carbon-mercury bonds^{22,23} and might be termed an *Sei* reaction.



Experimental Section

The basic procedure used to prepare the substrates **3** was that of Ramart-Lucas.^{14,15} The following procedure is illustrative.

2,3-Diphenylbutyronitrile.—To 75 ml of anhydrous ether plus 4.0 g (0.16 g-atom) of magnesium in a dried 500-ml, round-bottom flask was added 10.0 ml (0.17 mol) of methyl iodide in 21 ml of ether dropwise with stirring over a period of 1 hr. To this solution was added 5.0 g (0.024 mol) of α -phenylcinnamionitrile

(19) H. E. Zimmerman and M. D. Traxler, *ibid.*, **79**, 1920 (1957).

(20) H. E. Zimmerman and H. Giallombardo, *ibid.*, **78**, 6259 (1956).

(21) G. A. Russell, *ibid.*, **81**, 2016 (1959).

(22) S. Winstein and T. G. Traylor, *ibid.*, **78**, 7592 (1956).

(23) F. R. Jensen and L. H. Gale, *ibid.*, **82**, 148 (1960).

(mp 82–84°) as a solid. The initial reaction was mildly exothermic and red coloration developed over a period of 15 min. The reaction mixture was stirred overnight.

Four quenching mixtures were prepared: (a) *ca.* 10 g of NH₄Cl in *ca.* 200 g of ice, (b) 20 ml of C₂H₅OH, (c) 10 ml of acetic acid in 20 ml of ether, and (d) 20 ml of ether into which anhydrous HCl had been passed for *ca.* 10 min. The reaction mixture was divided into four equal parts and added to each quenching solution (cooled in ice) by pipet. Owing to the excess of Grignard reagent the quenching was extremely exothermic. The C₂H₅OH mixture was immediately acidified and the solvent evaporated. Each reaction mixture was worked up rapidly by adding to ice and ether in a separatory funnel and shaking. The aqueous layer was reextracted with *ca.* 50 ml of ether. The combined ether layers were extracted twice with *ca.* 75 ml of H₂O to which several grams of NH₄Cl had been added. The ether solution was dried with MgSO₄ and filtered and the solvent evaporated through a Vigreux column. A small quantity of CCl₄ was added to the oil and this was evaporated. A portion of the oil was taken up in CCl₄ and analyzed by nmr spectroscopy; the results are given in Table III.

All oils were combined and concentrated. Upon standing the material partially crystallized. The crystals were recrystallized twice from CHCl₃, mp 132–134° (lit.¹⁴ 133). The remaining oil from which all possible solid has been crystallized was mainly the *threo* isomer contaminated with *ca.* 20% *erythro*. This material was chromatographed on silica gel and eluted with increasing quantities of benzene in hexane. All fractions were oils whose spectrum disclosed increasing quantities of the *erythro* isomer.²⁴

2,3-Diphenylvaleronitrile.—This material was prepared similarly again yielding a solid *erythro* isomer, mp 114.0–114.8°, and a noncrystalline mixture, predominately *threo*.

Anal. Calcd for C₁₇H₁₇N (*erythro*): C, 86.9; H, 7.3. Found: C, 86.71; H, 7.43.

2,3-Diphenyl-4-methylvaleronitrile.—The *erythro* isomer was a solid, mp 104.5–105.2°.

Anal. Calcd for C₁₈H₁₉N: C, 86.7; H, 7.68. Found: C, 86.63; H, 7.70.

2,3-Diphenyl-3-cyclohexylpropionitrile.—The *erythro* isomer was obtained by chromatography on silica gel with elution by 10% ether in pentane, mp 120–122°.

Anal. Calcd for C₂₁H₂₃N: C, 87.3; H, 8.02. Found: C, 87.09; H, 8.20.

The other fractions crystallized in part as mixtures of the two isomers. Repeated crystallization by the

triangle scheme afforded little purification. The best *threo* isomer obtained, mp 83–87°, still contained *ca.* 10% *erythro* by nmr.

2,3-Diphenyl-4,4-dimethylvaleronitrile.—The *erythro* isomer had mp 110.8–111.5°.

Anal. Calcd for C₁₉H₂₁N: C, 86.6; H, 8.03. Found: C, 86.50; H, 8.01.

The best melting point obtained for the *threo* isomer was 50–53°. Figure 2 shows a partial nmr spectrum of mixed *erythro* and *threo* diastereomers resulting from the NH₄Cl–ice quench.

3-Thiophenoxy-2,3-diphenylpropionitrile.—To 50 ml of a solution of sodium ethoxide (*ca.* 0.1 M) was added thiophenol, 10.3 g, 0.084 mol and 1, 12.0 g (0.03 mol). The solution was stirred at 50° for 2 days. An unidentified precipitate was filtered off, mp 204° dec. To the remainder Hg(NO₃)₂ was added until the smell of thiophenol was no longer evident. This precipitate was washed twice with 25-ml portions of ethanol and the solutions were evaporated to a small volume and crystallization induced yielding 3.0 g of the *erythro* isomer, mp 104–108°. This was taken up in ether, extracted twice with H₂O, dried with MgSO₄, filtered and recrystallized three times from ether-pentane, mp 114–115°.

Anal. Calcd for C₂₁H₁₇NS: C, 80.0; H, 5.44. Found: C, 79.93; H, 5.49.

The remainder of the ethanol solution was mainly the *threo* isomer by nmr. Crystallization could not be induced. Attempted chromatography produced 1 and thiophenol.

Equilibration Experiments.—Approximately 200 mg of the substrate was placed in a 20-ml portion of 0.06 M NaOCH₃ in CH₃OH and allowed to stand at room temperature for 2 days. The solution was poured into dilute HNO₃ and extracted twice with 50-ml portions of ether. The ether layer was extracted with three 50-ml portions of H₂O plus NaHCO₃, dried over MgSO₄, evaporated, taken up in CCl₄, and analyzed by nmr spectroscopy. The data in Table II represent the average of duplicate runs.

Registry No.—*erythro* 3 (R = CH₃), 5558-38-3; *erythro* 3 (R = C₂H₅), 15645-51-9; *erythro* 3 (R = *i*-C₃H₇), 15645-52-0; *erythro* 3 (R = *t*-C₄H₉), 15717-34-7; *erythro* 3 (R = S-C₆H₅), 15645-53-1; *erythro* 3 (R = C₆H₁₁), 15645-54-2; *threo* 3 (R = CH₃), 15645-55-3; *threo* 3 (R = C₂H₅), 15645-57-5; *threo* 3 (R = *i*-C₃H₇), 15645-56-4; *threo* 3 (R = *t*-C₄H₉), 15717-33-6; *threo* 3 (R = S-C₆H₅), 15645-58-6; *threo* 3 (R = C₆H₁₁), 15645-59-7.

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(24) Upon acidic hydrolysis, the *erythro* nitrile, mp 132–134°, produced predominately *erythro*-2,3-diphenylbutyric acid, mp 186–188°, whereas a mixture of the *erythro* and *threo* nitriles yielded a mixture of *erythro* and *threo* acids.⁶