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STEREOCHEMISTRY OF THE GLYOXYLATE N-SULFONYLIMINE ENE REACTION

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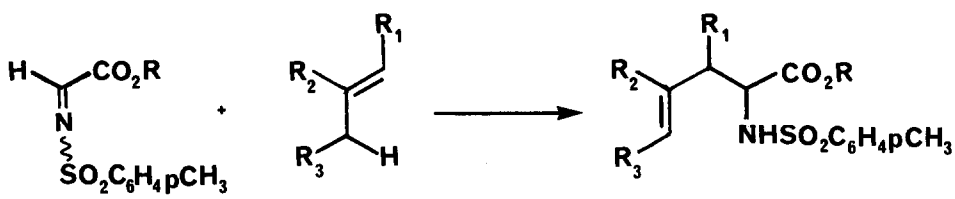
Summary: Ene reactions of sulfonylimine 1b with cyclohexene and trans-2-butene are highly stereoselective, affording products 4 and 10, respectively.

Recently, Achmatowicz reported that N-toluenesulfonylimine 1a derived from n-butyl glyoxylate undergoes facile ene reactions thermally or under Lewis acid catalysis to afford γ,δ-unsaturated-α-amino acid derivatives 2.[1] This reaction appears to offer a potentially

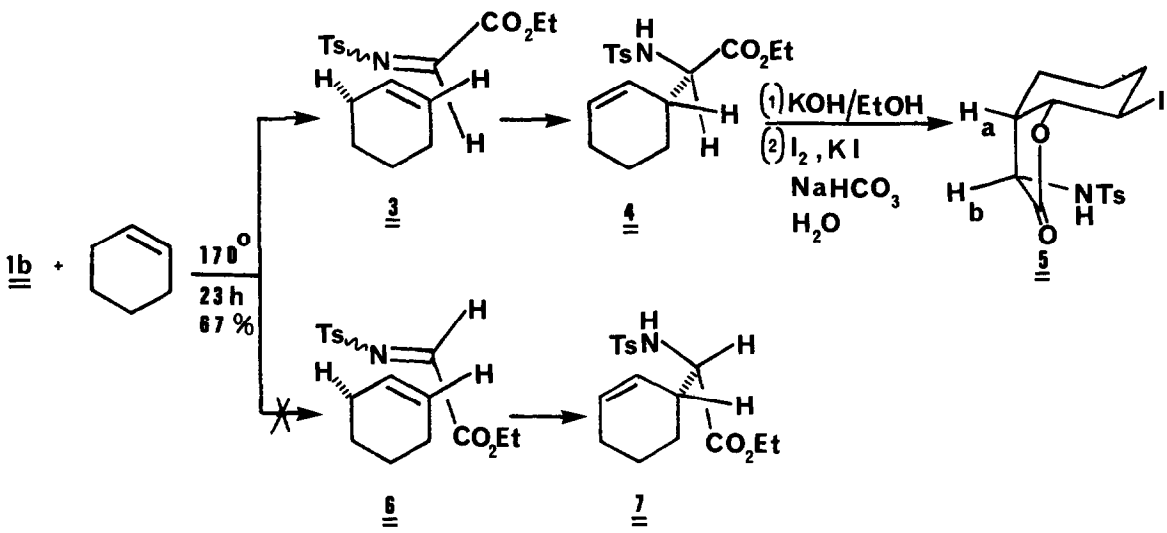


1a R=nBu
1b R=Et

2

efficient route to a variety of complex natural products containing amino acid functionality.[2] A few of the reported examples of addition of 1a to substituted alkenes ($R_1 \neq H$) lead to products of structure 2 which are capable of existing as diastereomers. However, no information was provided concerning the diastereoselectivity of the ene process. We now wish to report that the thermal reactions of 1 with cyclohexene and trans-2-butene are in fact highly stereoselective and afford products resulting primarily from ene transition states having the ester carbonyl group of 1 "endo".[3]

Heating imine 1b[4] in excess cyclohexene in a sealed tube at 170°C for 23 h provided a 67% yield of a single ene product as evidenced by ^{13}C NMR which proved to have structure 4.

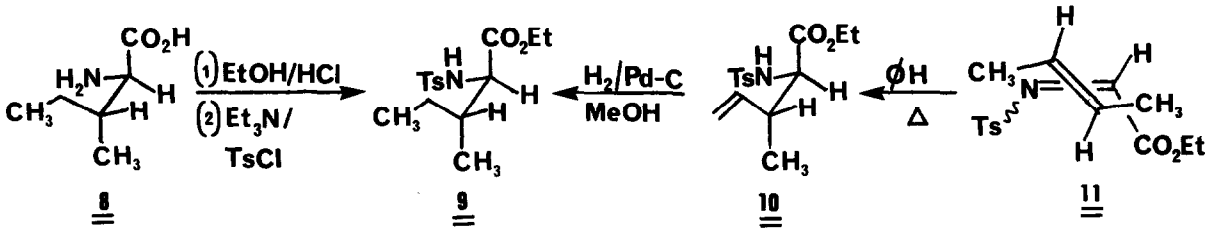


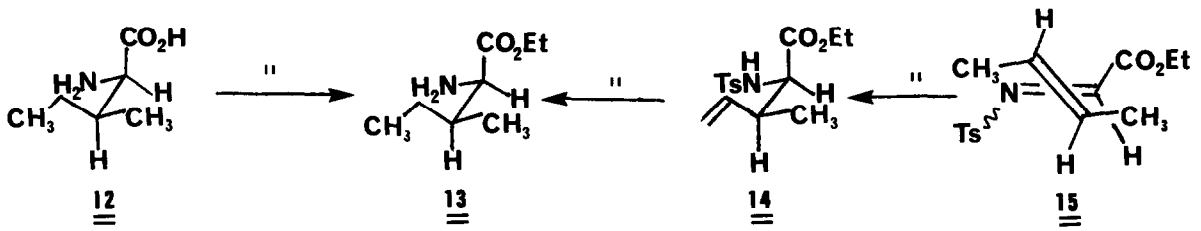
The stereochemistry of adduct 4 was established by its basic hydrolysis to the corresponding acid and subsequent iodolactonization to 5. Careful examination of the 360 MHz ^{1}H NMR spectrum of 5 confirmed the stereochemical assignment shown.[6] In particular, the 6.1 Hz coupling constant between H_a and H_b was in agreement with that reported for some very closely related systems by Bartlett[2a,8] and Snider.[7]

Thus, compound 4 is likely produced *via* transition state 3 having the carboethoxyl group "endo". None of the product 7 derived from the "exo" transition state 6 could be detected. The analogous thermal ene reaction of methyl glyoxylate with cyclohexene has been reported to go in very poor yield (5%).[7] Ferric chloride catalyzed addition was cleaner and gave mainly the product derived from an "endo" transition state like 3, although the stereoselectivity was poorer than in our thermal imino case. Interestingly, we have observed that Lewis acid catalyzed additions of 1b to cyclohexene affords mixtures of 4 and 7.

Thermal reaction of 1b with *trans*-2-butene was conducted in benzene in a sealed tube at 150°C for 20 h, affording an inseparable 9:1 mixture of 10 and 14, respectively (77% yield). The structures of these ene products were firmly established by chemical correlation with isoleucine and allo-isoleucine. Treatment of allo-isoleucine (8)[9] with EtOH/HCl, followed by tosyl

chloride/triethyl amine gave 9.[6] Similarly, 13 was prepared from isoleucine (12).[6] Hydrogenation of the mixture of adducts 10 and 14 afforded an inseparable mixture of 9 and 13, which was unambiguously correlated with the authentic amino acid derived samples by high field ^{1}H NMR and ^{13}C NMR. Thus, as in the cyclohexene reaction, it appears that the "endo" transition





state 11 is favored over the "exo" situation 15.

To our disappointment, cis-2-butene and 1b gave a 1.5:1 mixture of ene products 10 and 14, respectively. However, glc examination of recovered 2-butene indicated that about 1:1 mixture of cis and trans isomers was present. Careful purification of sulfonylimine 1b did not result in improved stereoselectivity. We are not certain what is causing double bond isomerization of the cis-2-butene, but clearly the lack of product selectivity is not the result of a stereorandom ene process.

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References

(1) Achmatowicz, O.; Pietraszkiewicz, M. J. Chem. Soc., Perkin I 1981, 2680.

(2) For an interesting Claisen rearrangement based approach to systems like 2 see: (a) Bartlett, P.A.; Barstow, J.F. Tetrahedron Lett. 1982, 623. (b) Bartlett, P.A.; Tanzella, D.J., Barstow, J.F. ibid. 1982, 619.

(3) For reviews of the ene reaction and its stereochemistry see: (a) Hoffman, H.M.R. Angew. Chem. Int. Ed. Engl. 1969, 8, 556.

(4) Prepared from ethyl glyoxylate[5] and N-sulfinyl-p-toluenesulfonamide: cf Albrecht, R.; Kresze, G. Chem. Ber. 1965, 98, 1431. 1b IR (film) 1735, 1630, 1600, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (3 H, t, J = 7.0 Hz), 2.50 (3 H, s), 4.40 (2 H, q, J = 7.0 Hz), 7.20 (2 H, d, J = 7.5 Hz), 7.68 (2 H, d, J = 8.30 Hz).

(5) We are grateful to American Hoechst Corporation for a generous supply of ethyl glyoxylate.

(6) Spectral data for selected compounds: 4:IR (KBr) 3250, 1700, 1600, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.06 (3 H, t, J = 7.32 Hz), 1.50 (2 H, m) 1.79 (2 H, m), 1.96 (2 H, m), 2.40 (3 H, s), 2.54 (1 H, m), 3.80 (1 H, dd, J = 10.38, 4.88 Hz), 3.87 (2 H, q, J = 7.32 Hz), 5.08 (1 H, d, J = 10.38 Hz), 5.43 (1 H, m), 5.85 (1 H, m), 7.27 (2 H, d, J = 7.94 Hz), 7.71 (2 H, d, J = 8.24 Hz); mass spectrum, m/e (relative intensity) 337 (1.1), 256 (57.9) 155 (96.3), 91 (85.8). 5: IR (KBr) 3250, 1790, 1600, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.26 (2 H, m), 2.45 (3 H, s), 3.16 (1 H, m), 3.97 (1 H, dd, J = 6.10, 3.66 Hz), 4.65 (1 H, m), 4.76 (1 H, m), 5.10 (1 H, d, J = 3.66 Hz), 7.35 (2 H, d, J = 7.94 Hz), 7.80 (2 H, d, J = 8.24 Hz); mass spectrum, m/e (relative intensity) 435 (0.3), 308 (4.8), 155 (59.8), 91 (100); exact mass calculated for $C_{15}H_{18}NO_4SI$: 435.0003; found: 435.0015. 9: IR (film) 3280, 1730, 1600, 1165; ^1H NMR ($CDCl_3$ 360 MHz) δ 0.82 (3 H, d, J = 6.71 Hz), 0.91 (3 H, t, J = 7.32 Hz), 1.06 (3 H, t, J = 7.02 Hz), 1.35 (2 H, m), 1.77 (1 H, m), 2.40 (3 H, s), 3.87 (1 H, dd, J = 6.56, 3.66 Hz), 3.88 (2 H, q, J = 7.02 Hz), 5.30 (1 H, d, J = 9.77 Hz); ^{13}C NMR δ 171.49, 143.46, 136.84, 129.48, 127.35, 61.37, 59.12, 38.14, 25.93, 21.43, 14.21, 13.89, 11.46; mass spectrum m/e (relative intensity) 313 (0.4), 240 (100), 91 (61.6). 13: IR (film) 3280, 1730, 1600, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz), δ 0.87 (3 H, t, J = 7.32 Hz), 0.91 (3 H, d, J = 7.02 Hz), 1.07 (3 H, t, J = 7.02 Hz), 1.29 (2 H, m), 1.78 (1 H, m), 2.41, (3 H, s), 3.75 (1 H, dd, J = 9.77, 5.12 Hz), 3.88 (2 H, q, J = 7.02 Hz), 5.16 (1 H, d, J = 9.77 Hz), 7.28 (2 H, d, J = 8.54 Hz), 7.72 (2 H, d, J = 8.54 Hz); ^{13}C NMR δ 171.19, 143.44, 136.75, 129.48, 127.29, 61.27, 60.20, 38.47, 24.63, 21.43, 15.32, 13.77, 11.23; mass spectrum m/e (relative intensity) 313 (0.1), 240 (100), 91 (99.4).

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(8) Bartlett, P.A.; Pizzo, C.F. J. Org. Chem. 1981, 46, 3896.

(9) Isoleucine and allo-isoleucine were obtained from Sigma Chemical Company.

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