Stereochemistry in Nucleophilic Vinylic Substitution of Activated Nitro Olefins. 2[1]

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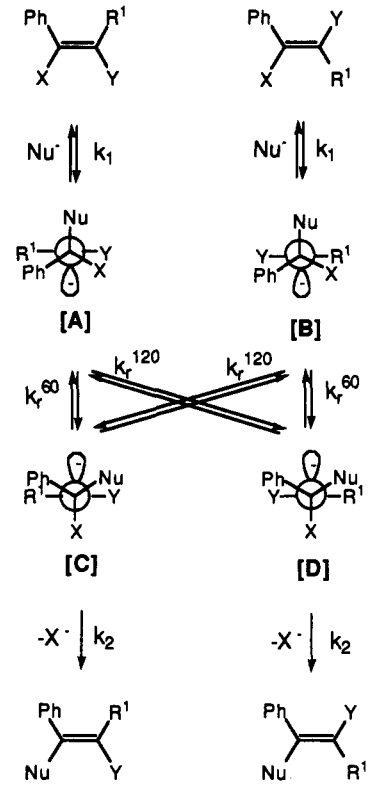
Some nucleophilic vinylic substitutions[2] proceed through rate-determining addition of nucleophile (k_1) to make the carbanion intermediate[3] followed by elimination of nucleofuge (k_2) as in Scheme I. The stereochemistry of this addition–elimination reaction observed as retention, inversion, or convergence gives some insight into the mechanistic detail not available in kinetic studies.[4] The configuration of the product relative to that of the starting olefin is dependent on the rate of internal rotation (k_r) relative to the rate of expulsion (k_2).[2d] With good nucleofuges complete retention is observed[5] since $k_2 > k_r$, and negative hyperconjugation[6] causes $k_r^{60} > k_r^{120}$. On the other hand, reactions with poor nucleofuges result in mostly stereoconvergence since $k_2 < k_r$.[7]

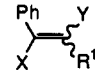
In a previous paper, the stereochemical course of nucleophilic vinylic substitution with α,β-dinitroolefins such as 2,3-dinitro-2-butene, 3,4-dinitro-3-hexene, and α,β-dinitrostilbene has been studied. Their reactions with amines and thiocyanate as nucleophiles yielded only *Z* isomers of vinylic-substituted nitroolefins.[1] This observation was explained by attractive interaction between the remaining nitro group and the appended nucleophile in the conformation leading to products. In considering conformations such as described in the Scheme I, one had to assume equal opportunity for the nucleophile to approach from both above and below the plane of the backbone. Approach of the nucleophile (Nu^-) from the top of *Z* isomer would form the conformational intermediate [**A**]. The same conformational intermediate would be formed by attack of nucleophile from the bottom on the *E* isomer. Likewise, the conformational intermediate [**B**] could be assumed from attack of the nucleophile from the top on the *E* isomer and from the bottom on the *Z* isomer. This line of reasoning would result in two reasonably stable conformational intermediates [**A**] and [**B**]. Under the condition of $k_r > k_2$, rotation about the former double bond could generate conformational intermediates [**C**] and [**D**], where the leaving nucleofuge was ready to be expelled parallel to the p orbital of the carbon bearing the remaining nitro group (Y = NO_2). From these conformational intermediates only the *Z* product would be formed if a heteroatom of the appended nucleophile associated attractively with the oxygen atoms of the remaining nitro group via the conformational intermediate [**C**]. With *p*-toluenethiolate as nucleophile, partial conversion was observed due to weaker interaction compared to thiocyanate and amines while the latter gave complete conversion to *E* isomers.

If there is steric and/or electrostatic repulsive interaction between the nucleophile and Y group, the conformational intermediate [**D**] will be preferred, resulting exclusively in *E* product. To prove this idea, (*E*)- and (*Z*)-methyl α-bromo-β-nitrocinnamate (**2**) and (*E*)-4-phenyl-4-nitro-3-bromo-3-buten-2-one (**5**) were synthesized and reacted with thiocyanate as a nucleophile.

Scheme I[a]



[a] X = leaving group, Y = activating group, Nu = nucleophile.



1 $R^1 = CO_2CH_3$, X = H, Y = Br
2 $R^1 = CO_2CH_3$, X = NO_2, Y = Br
3 $R^1 = CO_2CH_3$, X = Y = SCN
4 $R^1 = COCH_3$, X = H, Y = Br
5 $R^1 = COCH_3$, X = NO_2, Y = Br
6 $R^1 = COCH_3$, X = Y = SCN

(*E*)- and (*Z*)-methyl α-bromocinnamates (**1**) were prepared by the known method.[8] The *E* and *Z* isomers were nitrated separately with nitric acid and sodium nitrite to yield an *E*/*Z* mixture of methyl α-bromo-β-nitrocinnamate (**2**) in a variable ratio of 5:1 to 8:1. Bromination and dehydrobromination of (*E*)-4-phenyl-3-buten-2-one gave

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(1) Part 1: Park, K. P.; Ha, H.-J. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3006.
(2) For reviews, see: (a) Rappoport, Z. *Adv. Phys. Org. Chem.* **1969**, *7*, 1. (b) Modena, G. *Acc. Chem. Res.* **1971**, *4*, 73. (c) Miller, S. I. *Tetrahedron* **1977**, *33*, 1211. (d) Rappoport, Z. *Acc. Chem. Res.* **1981**, *14*, 7. (e) Rappoport, Z. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 309. (f) Shainyan, B. A. *Usp. Khim.* **1986**, *55*, 942.
(3) A reaction intermediate of nucleophilic vinylic substitution was observed under conditions conductive to substitution: Bernasconi, C. F.; Fassberg, J.; Killion, R. B., Jr.; Rappoport, Z. *J. Am. Chem. Soc.* **1990**, *112*, 3169.
(4) For a comprehensive review, see: Bernasconi, C. F. *Tetrahedron* **1989**, *45*, 4017.
(5) Retention may also be explained as the stereochemical outcome for the single-step process: Texier, F.; Henri-Rousseau, O.; Bougois, J. *Bull. Soc. Chim. Fr.* **1979**, *2*, 86.
(6) Apeloig, Y.; Rappoport, Z. *J. Am. Chem. Soc.* **1979**, *101*, 5095.
(7) (a) Rappoport, Z.; Avramovitch, B. *J. Org. Chem.* **1982**, *47*, 1397. (b) Rappoport, Z.; Gazit, A. *J. Org. Chem.* **1985**, *50*, 3184. (c) Rappoport, Z.; Gazit, A. *J. Org. Chem.* **1986**, *51*, 4112. (d) Rappoport, Z.; Gazit, A. *J. Am. Chem. Soc.* **1987**, *109*, 6698. (e) Avramovitch, B.; Rappoport, Z. *J. Am. Chem. Soc.* **1988**, *110*, 911. (f) Lodder, G.; van Drop, J. W. J.; Avramovitch, B.; Rappoport, Z. *J. Org. Chem.* **1989**, *54*, 2574. (g) Rappoport, Z.; Topol, A. *J. Org. Chem.* **1989**, *54*, 5967.
(8) (a) Sudborough, J. J.; Thompson, K. J. *J. Chem. Soc.* **1903**, *83*, 666. (b) Singer, L. A.; Kong, N. P. *Tetrahedron Lett.* **1967**, 643. (c) Klein, J.; Zitrin, S. *J. Org. Chem.* **1970**, *35*, 666.

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(*E*)- and (*Z*)-4-phenyl-3-bromo-3-buten-2-one (**4**) in 74% yield in a 9:2 ratio. The neat *Z* isomer slowly converted to the *E* isomer upon standing at room temperature. (*E*)- and (*Z*)-4-Phenyl-3-bromo-3-buten-2-one were nitrated separately with nitric acid and sodium nitrite to give a single nitrated product, (*E*)-4-phenyl-4-nitro-3-bromo-3-buten-2-one (**5**), which was characterized by X-ray crystallography.[9]

Substitution reactions of (*E*)- and (*Z*)-methyl α-bromo-β-nitrocinnamate (**2**) and (*E*)-4-phenyl-4-nitro-3-bromo-3-buten-2-one (**5**) with thiocyanate as a nucleophile were anticipated to yield methyl α-thiocyanato-β-nitrocinnamate and 4-phenyl-4-nitro-3-thiocyanato-3-buten-2-one. Instead these reactions gave single geometric isomers of disubstituted products, (*E*)-methyl α,β-dithiocyanatocinnamate (**3**) and (*E*)-4-phenyl-3,4-dithiocyanato-3-buten-2-one (**6**) in good yield.[10] Using less than 1 equiv of thiocyanate relative to the substrate, we observed the same disubstituted product exclusively. This report is the first example that nucleophilic vinylic substitution reaction occurs twice at α and β carbons of the same substrate olefin without formation of detectable amounts of monosubstituted product.[11]

At first, 1 equiv of thiocyanate adds to the substrate (**2**, **5**) at the α-position activated by both nitro and carbonyl groups to make a carbanion intermediate. This is followed by the elimination of the nucleofuge (Br^-) to yield the monosubstituted products, presumably methyl α-thiocyanato-β-nitrocinnamate and 4-phenyl-3-thiocyanato-4-nitro-3-buten-2-one. These products are apparently more reactive toward nucleophilic substitution than the starting substrates due to additional activation by the thiocyanato group relative to bromine.[2a] Another equivalent of thiocyanate adds to make conformational intermediates [**C**] and [**D**], wherein $R^1 = CO_2CH_3$ or $COCH_3$, X = NO_2, Y = SCN, Nu = SCN (Scheme I). Here, it is expected that two sulfur atoms nearby might be quite repulsive since the sulfur atom in the thiocyanato group might bear some positive partial charge due to electron-withdrawing cyano group in it. Thus the conformational intermediate [**D**] would be preferred, resulting only in the *E* product. Also noteworthy is the fact that in this conformation, there may be extra stabilization by the attractive interaction between the oxygen atom of carbonyl group and the sulfur atom of the thiocyanato group.

Along with the earlier result, we conclude that the stereochemical outcome of some nucleophilic vinylic substitution reactions is determined by interactions between the activating groups of the substrate and the appended nucleophile.

Experimental Section

General. ^1H NMR spectra were recorded with either a Varian EM60 (60 MHz) or a JEOL JNM-PMX 60-S1 (60 MHz) spectrophotometer. ^{13}C NMR spectra were recorded with a Bruker Ap-20 OSY (50.3 MHz) spectrophotometer. Chemical shifts were given in ppm using TMS as internal standard. IR spectra were recorded with a FX-6160 KTIR spectrophotometer. Melting points are uncorrected and were determined with a Thomas-Hoover apparatus. All reagents were used without further purification unless specified. The silica gel used for column chromatography was Merck 200–230 mesh. Thin-layer chromatography was carried out with Merck 60F-254 plates with 0.25-mm thickness. Mass spectra were obtained on a Hewlett Packard Model 5985B spectrometer. Microanalyses were obtained on a Perkin-Elmer 240 DS element analyzer.

(*E*)- and (*Z*)-Methyl α-Bromocinnamate (1). (*E*)- and (*Z*)-**1** were prepared by following the known method.[8]

(*E*)- and (*Z*)-Methyl α-Bromo-β-nitrocinnamate (2). To either (*E*)- or (*Z*)-**1** (1.0 g, 4.1 mmol) was added nitric acid (5 mL) at −5 °C. The resultant mixture was stirred vigorously before slow addition of sodium nitrite (0.52 g, 7.5 mmol) in small portions. The reaction mixture was stirred at −5 °C for 10 min. After removal of cooling bath, the reaction mixture was stirred at room temperature for 4 h before quenching the reaction by adding saturated $NaHCO_3$ solution. The reaction mixture was neutralized by adding saturated $NaHCO_3$ solution and the reaction product was extracted with CH_2Cl_2. The organic layer was washed successively by water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give (*E*)- and (*Z*)-methyl α-bromo-β-nitrocinnamate in a 5:1–8:1 ratio in 45% yield. Each isomer was isolated and purified by column chromatography. (*E*)-**2**: ^1H NMR ($CDCl_3$) 3.93 (s, 3 H), 7.69 (bs, 5 H); IR (neat) 519, 1266, 1545, 1743 cm^{-1}; MS (70 eV), *m/z* (rel intensity) 287 (M^+, 3), 285 (M^+, 3), 241 (28), 239 (33), 181 (14), 179 (13), 129 (100), 116 (45), 105 (94). Anal. Calcd for $C_{10}H_8BrNO_4$: C, 41.9; H, 2.81; N, 4.89. Found: C, 42.1; H, 2.88; N, 4.85. (*Z*)-**2**: ^1H NMR ($CDCl_3$) 3.90 (s, 3 H), 7.51 (bs, 5 H); IR (neat) 488, 1271, 1536, 1735 cm^{-1}; MS (70 eV), *m/z* (rel intensity) 287 (M^+, 4), 285 (M^+, 4), 241 (51), 239 (79), 181 (44), 179 (32), 129 (100), 116 (99), 115 (87), 105 (72). Anal. Calcd for $C_{10}H_8BrNO_4$: C, 41.9; H, 2.81; N, 4.89. Found: C, 42.2; H, 2.79; N, 4.92.

(*E*)-Methyl α,β-Dithiocyanatocinnamate (3). Sodium thiocyanate (1.02 g, 12.6 mmol) was added into a solution of (*E*)- or (*Z*)-**2** (1.21 g, 4.2 mmol) dissolved in 10 mL of ethanol. The reaction mixture was stirred at room temperature for 3 h. After observing that all starting material on TLC was consumed, the solvent was removed under reduced pressure to dryness. The reaction product was dissolved with EtOAc and water. The organic layer was washed with water and brine successively, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The reaction product was purified by column chromatography and recrystallized to give a crystalline product (0.87 g) in 75% yield: mp 105–106 °C; ^1H NMR ($CDCl_3$) 3.95 (s, 3 H, methyl), 7.2–7.7 (m, 5 H, phenyl); IR 722, 1283, 1441, 1556, 1696, 2163 cm^{-1}. Anal. Calcd for $C_{12}H_8N_2S_2O_2$: C, 52.1; H, 2.91; N, 10.1. Found: C, 52.2; H, 2.89; N, 9.85. The reactions with 0.7 and 0.5 molar equiv of sodium thiocyanate relative to the substrate **2** gave **3** in 28% and 20% yields, each with the recovery of starting material.

(*E*)- and (*Z*)-4-Phenyl-3-bromo-3-buten-2-one (4). (*E*)-4-Phenyl-3-buten-2-one (29.2 g, 0.2 mol) purchased from Aldrich was brominated in methylene chloride with bromine (32 g, 10.3 mL, 0.2 mol) at 0 °C. The reaction mixture was concentrated under reduced pressure and purified by recrystallization with *n*-hexane to yield 55.7 g of 4-phenyl-3,4-dibromobutan-2-one in 91% yield: ^1H NMR ($CDCl_3$) 2.49 (s, 3 H, CH_3), 4.97 (d, J = 12 Hz, 1 H, CHBr), 5.43 (d, J = 12 Hz, 1 H, CHBr), 7.52 (s, 5 H, phenyl). Triethylamine (30.4 g, 0.3 mol) was added to 4-phenyl-3,4-dibromobutan-2-one (30.6 g, 0.1 mol) in 250 mL of THF. The resultant reaction mixture was refluxed for 1 h before quenching the reaction by adding 200 mL of water. The reaction product was extracted with THF. The organic layer was washed successively with water, 1 N HCl, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The reaction product was purified by column chromatography to yield (*E*)- and (*Z*)-**4** in 14.9 g (66%) and 3.29 g (15%) each. (*E*)-**4**: ^1H NMR ($CDCl_3$) 2.51 (s, 3 H, CH_3), 7.32–7.51 (m, 3 H, phenyl), 7.75–8.04 (m, 2 H, phenyl), 8.05 (s, 1 H, olefinic); ^{13}C NMR ($CDCl_3$) 26.6, 123.4, 128.4, 130.2, 130.3, 133.7, 139.8, 192.7. Anal. Calcd for $C_{10}H_9BrO$: C, 53.3; H, 4.03. Found: C, 53.4; H, 4.07. (*Z*)-**4**: ^1H NMR ($CDCl_3$) 2.20 (s, 3 H, CH_3), 7.38 (bs, 6 H, phenyl and

(9) Ha, H.-J.; Park, K. P.; Jeong, J. H. Submitted to *Bull. Kor. Chem. Soc.*

(10) Configuration of methyl α,β-dithiocyanatocinnamate was confirmed as *E* by X-ray crystallography. The configuration of 4-phenyl-3,4-dithiocyanato-3-buten-2-one was tentatively assigned to be *E* by comparison of spectral data with (*E*)-α,β-dithiocyanatocinnamate.

(11) A few tandem geminal and vicinal vinylic disubstitution reactions have been reported: Shainyan, B. A.; Mirskova, A. N. *Zh. Org. Khim.* **1980**, *16*, 1797, 2569 (for gemial); Andreini, B. P.; Benetti, M.; Carpita, A.; Rossi, R. *Gazz. Chim. Ital.* **1988**, 118, 469 (for vicinal). In the latter reference, (*E*)-1,2-dibromomethylene in the presence of *Z* isomer gave (*E*)-dialkynylethylene by addition of akylylzinc chloride with the assistance of Pd catalyst. This reaction is similar to ours in that reaction occurs twice at α and β carbons without formation of detectable amount of monosubstituted product.

olefinic); ^{13}C NMR ($CDCl_3$) 28.7, 120.8, 128.4, 128.5, 128.9, 134.6, 136.8, 197.2. Anal. Calcd for $C_{10}H_9BrO$: C, 53.3; H, 4.03. Found: C, 53.2; H, 3.98.

(*E*)-4-Phenyl-4-nitro-3-bromo-3-buten-2-one (5). To either (*E*)- or (*Z*)-4 (15.5 g, 69 mmol) was added nitric acid (50 mL) at −5 °C. The resultant mixture was stirred vigorously before slow addition of sodium nitrite (9.16 g, 133 mmol) in small portions for 30 min. The reaction mixture was stirred at −5 °C for 30 min. After removal of cooling bath the reaction mixture was stirred at room temperature for 10 h before quenching the reaction by adding saturated $NaHCO_3$ solution. The reaction mixture was neutralized by adding saturated $NaHCO_3$ solution, and the reaction product was extracted with CH_2Cl_2. The organic layer was washed successively with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The reaction product (*E*)-5 was purified by column chromatography and recrystallized with CH_2Cl_2–hexane to give a yellow crystalline produce (7.2 g, 38%): mp 66–68 °C; ^1H NMR ($CDCl_3$) 2.6 (s, 3 H, methyl), 7.72 (s, 5 H, phenyl); IR 722, 1183, 1526, 1711, 2163 cm^{-1}. Anal. Calcd for $C_{10}H_8N_1O_3Br$: C, 44.4; H, 2.98; N, 5.18. Found: C, 44.6; H, 2.95; N, 4.90.

(*E*)-4-Phenyl-3,4-dithiocyanato-3-buten-2-one (6). Sodium thiocyanate (0.9 g, 11.1 mmol) was added into a solution of (*E*)-5 (1.0 g, 3.7 mmol) dissolved in 10 mL of ethanol. The reaction mixture was stirred at room temperature for 3 h. After observing that all starting material on TLC was consumed, the solvent was removed under reduced pressure to dryness. The reaction product was dissolved with EtOAc and water. The organic layer was combined, washed with water and brine successively, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The reaction product was purified by column chromatography and recrystallized to give a crystalline product (0.53 g) in 55% yield: mp 103–104 °C, ^1H NMR ($CDCl_3$) 2.78 (s, 3 H, methyl), 7.31–7.78 (m, 5 H, phenyl); IR 736, 1242, 1361, 1480, 1522, 1664, 2157 cm^{-1}. Anal. Calcd for $C_{12}H_8N_2S_2O$: C, 55.3; H, 3.09; N, 10.7; S, 24.6. Found: C, 55.3; H, 3.05; N, 10.5; S, 24.6. The reactions with 0.7 and 0.5 molar equiv of sodium thiocyanate relative to the substrate 5 gave 6 in 17% and 10% yield; each with the recovery of starting material.

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Registry No. (*E*)-1, 24127-62-6; (*Z*)-1, 21788-36-3; (*E*)-2, 136132-16-6; (*Z*)-2, 136132-17-7; (*E*)-3, 136132-19-9; (*E*)-4, 31207-17-7; (*Z*)-4, 22965-96-4; (*E*)-5, 136132-18-8; (*E*)-6, 136132-20-2; (*E*)-4-phenyl-3-buten-2-one, 1896-62-4.

Supplementary Material Available: X-ray crystallographic data for compound 3 including experimental details, a computer-generated plot of the crystallographic asymmetric unit, and tables of isotopic and anisotropic thermal parameters, bond distances, and bond angles (5 pages). Ordering information is given on any current masthead page.

Additions and Corrections

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Alfred Hassner,* Simha Naidorf-Meir, and John Dillon. α-Substituted Cyclobutanones as Protecting Groups for Carboxylic Acids.

Page 4954. John Dillon's name was inadvertently omitted from the list of authors.

Duy H. Hua,* S. Narasimha Bharathi, Fusao Takusagawa, Jagath A. K. Panangadan, Mu-Huang Hung, Ana A. Bravo, and Angela M. Erpelding. Stereoselective Addition Reactions of Chiral α-Sulfinyl Ketimine Anions with Ene Esters. Facile Asymmetric Synthesis of Indolo[2,3-*a*]quinolizidine and Yohimbanoid Alkaloids.

Pages 5660–5661: The stereochemical assignments of compounds 3, 16, 17, 18a, and 18b and products from their subsequent transformations are incorrect.

Compound 3: Johns et al. (*Aust. J. Chem.* **1966**, *19*, 1951) reported a rotation of −12.5° for this compound. Under Registry no. 4802-79-3 for this compound, we found no references on the synthesis of optically active 3. Professor A. I. Meyers has brought to our attention the fact that the −12.5° value was found to be erroneous and the more recent literature values are as follows: −86.5°, −84°, and −85° (Meyers, A. I.; Sahda, T.; Loewe, M. F. *J. Org. Chem.* **1986**, *51*, 3108 and references cited therein).

We mistakenly reported our value as −14°: the value we observed was −19.14°. This value is inconsequential, however, because we have now found that our isolated 3 was enantiomerically impure (vide infra). We also reported 3 as the *R* enantiomer (the major isomer); Professor Meyers pointed out that ours was the *S* enantiomer.

Compounds 16 and 17: Reduction of 15 with $NaCNBH_3$ was stated as being stereoselective to give 16 exclusively. We have now found that the diastereomeric syn hydrogenation product is also formed, but because of its poor solubility in the chromatographic solvent system we used, it was neither detected nor isolated in our chromatographic procedure but constituted an impurity in 16. Thus, 17 and 3 became contaminated with their respective enantiomers, of which we were unaware.

Compounds 18a and 18b: As stated, these compounds were believed to be rotamers on the basis of the results noted in ref 25. Further investigation showed them to be diastereomers, to which the reaction and products noted in the reference must be reassigned.

These errors have now been corrected and the proper data and results have been incorporated into a forthcoming article in this journal.