Highly Stereoselective Preparation of Nitro Olefins and Nitro Dienes by the Addition-Elimination of Copper-Zinc Organometallics to β-Alkylthio and β-Phenylsulfonyl Nitro Olefins

Carole Retherford and Paul Knochel*

The Willard H. Dow Laboratories, Department of Chemistry, University of Michigan
Ann Arbor, Michigan 48109

Summary: The addition-elimination of copper-zinc organometallics $RCu(CN)ZnX$ to (E)-1-nitro-2-phenylsulfonyl ethylene $2a$ gave highly functionalized pure (E) nitro olefns and stereoselectively (1E, 3E) and (1E, 3Z)-1-nitro-dienes in excellent yields. Nitro olefns having a leaving group in β-position such as a dialkylamino-3, an alkylthio-4 or a phenylsulfonyl-5-group have been known to undergo addition-elimination-6 reactions with nucleophiles. Although β-nitroenamines are able to react with strong nucleophiles (RMgX, RLi), only the reaction of β-sulfur-substituted nitro olefins with weak nucleophiles (amines, enolates) has been reported. We have now found that β-sulfur-substituted nitro olefns of type 2 react under very mild conditions with the copper organometallics $1$ affording polyfunctional nitro olefins of type 3 in excellent yields-7 (Scheme I and Table I). Thus the addition of (E)-1-nitro-2-phenylsulfonylethylene $2a$ (1 eq.) to a THF solution of $RCu(CN)ZnX$ (1 eq.) at -78 °C furnishes, after warming the reaction mixture to -50 °C for 5 min., the stereoisomerically pure (E)-nitro olefns $3a-3d$ in 79-87% yields (entries 1-4 of Table I). The α-acetoxy copper-zinc reagent $1e$, readily prepared from isobutyraldehyde, acetyl bromide and zinc8, allows a unique approach to the interesting γ-nitro allylic acetates of type $3e$ (entry 5). The cyclic reagent 2-ethylthio-1-nitro-1-cyclohexene $2b$ displays the same type of reactivity, although the addition of $RCu(CN)ZnI$ proceeds only at higher temperatures (-20 ° to 25 °C) allowing the preparation of polyfunctional nitrocyclohexenes bearing functional groups such as an ester-, a cyano-, or a phosphonate9 group in 79-89% yields (entries 8, 9, 10). A highly stereoselective preparation of conjugated 1-nitro-1,3-dienes is also possible. The reaction of the (Z)-alkenylcopper reagent $1f$ prepared from (Z)-1-iodo-1-hexene10 with $2a$ gives (1E, 3Z)-1-nitro-1,3-octadiene $3f$ in 98% stereoisomeric purity. This nitro diene11 rapidly isomerizes during a flash chromatography purification; however, its distillation (42 °C, 0.03 mmHg) affords a 96% isomerically pure material in 82% yield (entry 6). Similarly, the reaction of $2a$ with the (E)-alkenylcopper compound $1g$ provides (1E, 3E)-1-nitro-1,3-decadiene $3g$ in 97% stereoisomeric purity (before chromatography) and 81%
yield (entry 7). The cyclic nitro diene 3k is obtained in 90% yield by the addition of the (E)-alkenylcopper 1g to 2-ethylthio-1-nitro-1-cyclohexene 2b (entry 11). The Michael addition of the 1,3-dienylcopper reagent to 2a gives the intermediate nitrotrien 5 which after a short path filtration over silica gel was stirred in hexane over silica gel for 4 hours affording the intramolecular cycloadduct 6 as a single diastereoisomer in 85% yield. This remarkably mild Diels-Alder reaction proceeds exclusively via an anti transition state (Scheme II). The silica gel catalysis is essential since the thermic cycloaddition has been shown to be non-stereospecific.

\[ \text{Scheme II} \]

The reaction of 2a with more sterically hindered secondary reagents did not take the expected course. Thus, the reaction of 2a (1 eq.) with the lithium ester enolate 7 (1.05 eq.) afforded as sole product the vinylic sulfone 8 in 75% yield (THF, -78 °C, 5 min.; Scheme III). Also, the addition of the copper reagent 9 derived from cyclohexylzinc iodide gave a mixture of the phenylsulfonyl substitution product 10 and the nitro substitution product 11 in 87% yield (10/11, 19:81).

\[ \text{Scheme III} \]

β-Disubstituted nitro olefins of type 13, which can usually not be prepared via a nitro aldol reaction (due to the reversibility of this reaction when ketones are used as substrates), are readily obtained by the reaction of commercially available 2,2-dimethylthio-1-nitroethylene 12 (1 eq.) with the copper reagents FG–RCu(CN)ZnI ((3 eq.), -78 °C to -30 °C, 4 h) in good yields (72-90%; Scheme IV). By using the dicopper reagent IZn(CN)Cu(CH₂)₄Cu(CN)ZnI which is available in high yield from 1,4-diiodobutane (zinc dust (2.5 eq.), 40 °C, 2 h), (nitromethylidene)cyclopentane is obtained in 85% yield.

In conclusion, we have shown that a variety of highly functionalized nitro olefins are available by the addition-elimination of RCu(CN)ZnI to β-alkylthio and β-phenylsulfonyl nitro olefins in good to excellent yields. Extensions of these reactions are currently underway.
Table I. Preparation of Polyfunctional Nitro Olefins and Nitro Dienes 3a-3k by the Reaction of (E)-1-nitro-2-phenyl sulfonylethylene 2a or 2-ethylthio-1-nitro-1-cyclohexene 2b with RCu(CN)ZnX.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Organocopper reagent</th>
<th>β-substituted nitro olefin</th>
<th>Products of Type 3</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtO$_2$(CH$_2$)$_3$Cu(CN)ZnI</td>
<td>1a</td>
<td>PhSO$_2$NO$_2$ 2a</td>
<td>3a</td>
</tr>
<tr>
<td>2</td>
<td>Ph$_2$=Cu(CN)ZnI</td>
<td>1b</td>
<td>2a</td>
<td>3b</td>
</tr>
<tr>
<td>3</td>
<td>NC(CH$_2$)$_2$Cu(CN)ZnI</td>
<td>1c</td>
<td>2a</td>
<td>3c</td>
</tr>
<tr>
<td>4</td>
<td>NC(CH$_2$)$_2$Cu(CN)ZnI</td>
<td>1d</td>
<td>2a</td>
<td>3d</td>
</tr>
<tr>
<td>5</td>
<td>Me$_2$Cu(CN)ZnBr</td>
<td>1e</td>
<td>2a</td>
<td>3e</td>
</tr>
<tr>
<td>6</td>
<td>Bu$_2$Cu(CN)ZnI</td>
<td>1f</td>
<td>2a</td>
<td>3f</td>
</tr>
<tr>
<td>7</td>
<td>Cu(CN)ZnI</td>
<td>1g</td>
<td>Hex</td>
<td>3g</td>
</tr>
<tr>
<td>8</td>
<td>1a</td>
<td></td>
<td></td>
<td>3h: R = (CH$_2$)$_2$CO$_2$Et</td>
</tr>
<tr>
<td>9</td>
<td>1d</td>
<td></td>
<td></td>
<td>3i: R = (CH$_2$)$_2$CN</td>
</tr>
<tr>
<td>10</td>
<td>(EtO)$_2$(O)P(CH$_2$)$_2$Cu(CN)ZnBr</td>
<td>1h</td>
<td></td>
<td>3j: R = (CH$_2$)$_2$P(O)(OEt)$_2$</td>
</tr>
<tr>
<td>11</td>
<td>1g</td>
<td></td>
<td></td>
<td>3k: R = (E)-CH=CH-Hex</td>
</tr>
</tbody>
</table>

a All yields refer to isolated yields of analytically pure products. Satisfactory spectral data (IR, $^1$H and $^{13}$C NMR, mass spectra, high resolution mass spectra) have been obtained for all compounds.

b The crude reaction mixture also contained ca. 10% of (E)-3-acetoxy-4-methyl-1-(phenylsulfonyl)-1-pentene.

c A (1E, 3Z)/(1E, 3E) mixture of 96:4 was obtained after distillation.

d The crude reaction mixture indicates a (1E, 3Z)/(1E, 3E) ratio of 98:2 which becomes 14:86 after flash chromatography.

e A (1E, 3Z)/(1E, 3E) mixture of 12:88 was obtained after flash chromatography.

f Obtained after flash chromatography as the pure (E)-isomer.

Acknowledgment: We thank the National Institutes of Health (GM-41908) for their generous support of this work and Dr. Peter Knoess for the preparation of some starting materials.

References and Notes:

5. (a) Ono, N., Kamimura, A.; Kaji, A. Tetrahedron Lett. 1986, 27, 1595; see also ref. 4a.


7. Typical procedure. (a) Improved preparation of (E)-1-nitro-2-phenylsulfonylethylene 2a. A mixture of (E)-1-nitro-2-phenylsulfonylethylene and 2a, the two following reactions were performed: (a) lithium ethanethiolate (3-cyanopropyl)copper derivative 1d prepared as reported previously. (b) Addition of RCu(CN)ZnI to β-sulfonyl nitro olefins. Preparation of 5-nitro-5-hexenenitrile 3d (entry 4 of Table I). A solution of 2a (1.28 g, 6 mmol) in 10 mL of THF was added dropwise at -78 °C to a THF solution of the reaction mixture was warmed to 25 °C and stirred 12 h at this temperature. The copper reagent 4 was prepared from 1-iodo-4,6-octadiene (zinc dust (3.0 eq.), THF, 40 °C, 4 h, > 85% yield); for the preparation of 4,6-octadienol to 1-iodo-4,6-octadiene: Scheffold, R.; Saladin, E. Tetrahedron Lett. 1984, 25, 1689.


10. (Z)-1-iodo-1-hexene (prepared according to Alexakis, A.; Cahiez, G.; Norman, J.F. J. Org. Synth. 1984, 62, 1) was converted to (Z)-1-iodo-1-hexene (Cahiez, G.; Bernard, D.; Norman, J.F. Synthesis 1976, 345) and treated successfully with zinc, NaOAc solution and brine, then dried over MgSO4. After evaporation of the solvent, the crude yellow solid was recrystallized from THF/hexane to give 7.77 g (73%) of analytically pure 2a. The attribution of the relative stereochemistry of di-tert-butylnitroxide (see: Komblum, N. Tetrahedron Lett. 1986, 27, 873.) was confirmed by additional NMR experiments: 3JH1, H2 = 12.5 Hz, 3JH2, H3 = 11.7 Hz, 3H2, H4 = 7 Hz. To confirm the assignment of the relative stereochemistry between H3 and H4, 6 was hydrogenated giving 3H3, H4 = 5 Hz (Scheme II); see (b) Roush, W.R. J. Am. Chem. Soc. 1980, 102, 1390; (c) Parlar, H.; Baumann, R. Angew. Chem. Int. Ed. Engl. 1981, 20, 1014; (d) Kurth, M.J.; O'Brien, M.J.; Hope, H.; Yanuck, M. J. Org. Chem. 1985, 50, 2626.


12. The copper reagent 4 was prepared from 1-iodo-4,6-octadiene (zinc dust (3.0 eq.), THF, 40 °C, 4 h, > 85% yield); for the preparation of 4,6-octadienol from sorbic acid see: (a) Jacobson, M. J. Am. Chem. Soc. 1985, 77, 2461; (b) Hudlicky, T.; Koszyk, F.J.; Kutchan, T.M.; Sheth, J.P. J. Org. Chem. 1980, 45, 5020; (c) for the conversion of 4,6-octadienol to 1-iodo-4,6-octadiene: Scheffold, R.; Saladin, E. Angew. Chem. Int. Ed. Engl. 1972, 11, 229.

13. (a) Ciganek, E. Org. React. 1984, 32, 1-374, John Wiley, New York. The attribution of the relative stereochemistry in compound 6 is based on the 1H NMR experiments: 3JH1, H2 = 11.5 Hz, 3JH2, H3 = 11.7 Hz, 3H2, H4 = 7 Hz. To confirm the assignment of the relative stereochemistry between H3 and H4, 6 was hydrogenated giving 3H3, H4 = 5 Hz (Scheme II); see (b) Roush, W.R. J. Am. Chem. Soc. 1980, 102, 1390; (c) Parlar, H.; Baumann, R. Angew. Chem. Int. Ed. Engl. 1981, 20, 1014; (d) Kurth, M.J.; O'Brien, M.J.; Hope, H.; Yanuck, M. J. Org. Chem. 1985, 50, 2626.

14. In order to prove a possible radical mechanism for the addition-elimination reaction of nucleophiles to (E)-1-nitro-2-phenylsulfonylethylene 2a, the two following reactions were performed: (a) lithium ethanethiolate was added at -78 °C to 2a. The solution was stirred for 5 min. and worked up as usual. (E)-2-ethylthio-1-nitro-2-phenylsulfonylethylene was obtained in a 1:4 ratio (75% yield); (b) the same reaction was performed in the presence of 5 mol % of di-tert-butylhydroperoxide (see: Kornblum, N. Angew. Chem. Int. Ed. Engl. 1975, 14, 734) leading to the same product distribution and ruling out a radical mechanism.