

## Highly Stereoselective Preparation of Nitro Olefins and Nitro Dienes by the Addition-Elimination of Copper-Zinc Organometallics to $\beta$ -Alkylthio and $\beta$ -Phenylsulfonyl Nitro Olefins

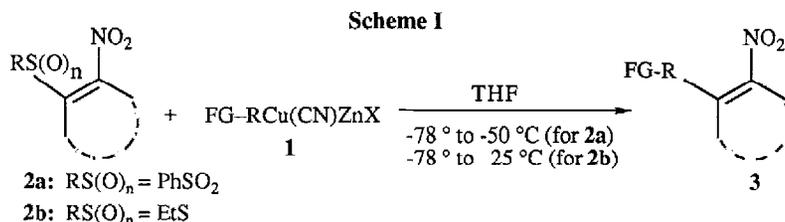
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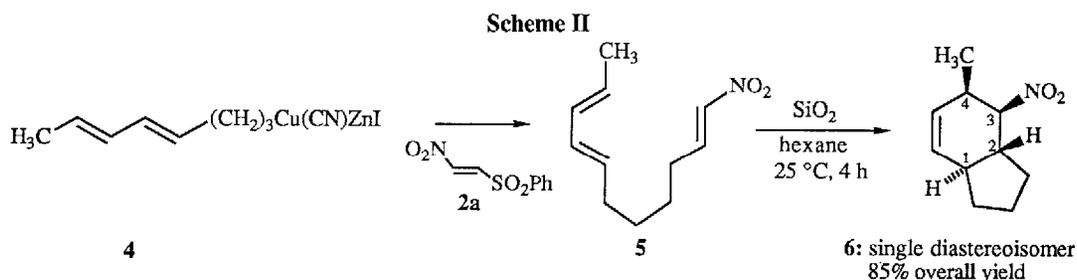
*Summary:* The addition-elimination of copper-zinc organometallics  $RCu(CN)ZnX$  to (*E*)-1-nitro-2-phenylsulfonyl ethylene **2a** gave highly functionalized pure (*E*) nitro olefins and stereoselectively (*1E, 3E*) and (*1E, 3Z*)-1-nitro-dienes in excellent yields.  $\beta$ -Alkylthio nitro olefins such as 2-ethylthio-1-nitro-1-cyclohexene **2b** and 2,2-dimethylthio-1-nitroethylene **12** were found to have a similar behavior. This methodology allowed an expedient preparation of the triene **5** which underwent an extremely mild silica gel-catalyzed, stereospecific Diels-Alder cyclization.

We have recently reported<sup>1</sup> that highly functionalized nitroalkanes can be prepared by the addition of a wide range of zinc-copper reagents<sup>2</sup> ( $RCu(CN)ZnX$ ) **1** to nitro olefins in high yields. Nitro olefins having a leaving group in  $\beta$ -position such as a dialkylamino-<sup>3</sup>, an alkylthio-<sup>4</sup> or a phenylsulfonyl<sup>5</sup>-group have been known to undergo addition-elimination<sup>6</sup> reactions with nucleophiles. Although  $\beta$ -nitroenamines are able to react with strong nucleophiles ( $RMgX$ ,  $RLi$ ), only the reaction of  $\beta$ -sulfur-substituted nitro olefins with weak nucleophiles (amines, enolates) has been reported. We have now found that  $\beta$ -sulfur substituted nitro olefins of type **2** react under very mild conditions with the copper organometallics **1** affording polyfunctional nitro olefins of type **3** in excellent yields<sup>7</sup> (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  $-78^\circ C$  furnishes, after

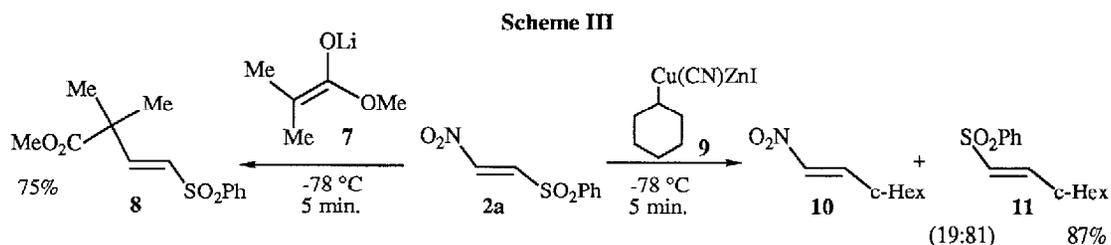


warming the reaction mixture to  $-50^\circ C$  for 5 min., the stereoisomerically pure (*E*)-nitro olefins **3a-3d** in 79-87% yields (entries 1-4 of Table I). The  $\alpha$ -acetoxy copper-zinc reagent **1e**, readily prepared from isobutyraldehyde, acetyl bromide and zinc<sup>8</sup>, allows a unique approach to the interesting  $\gamma$ -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 ( $-20^\circ$  to  $25^\circ C$ ) allowing the preparation of polyfunctional nitrocyclohexenes bearing functional groups such as an ester-, a cyano-, or a phosphonate<sup>9</sup> 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-hexene<sup>10</sup> with **2a** gives (*1E, 3Z*)-1-nitro-1,3-octadiene **3f** in 98% stereoisomeric purity. This nitro diene<sup>11</sup> rapidly isomerizes during a flash chromatography purification; however, its distillation ( $42^\circ C$ ; 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%

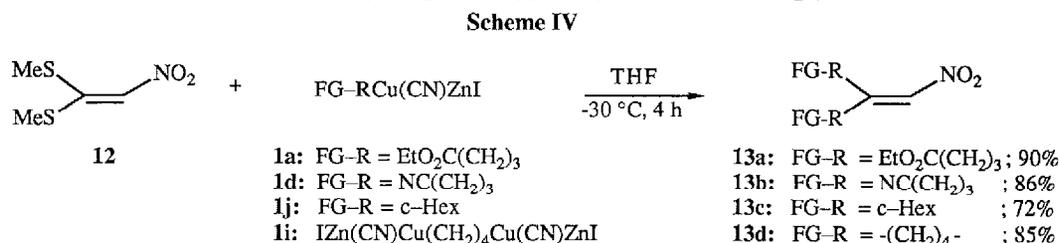
yield (entry 7). The cyclic nitro diene **3k** is obtained in 90% yield by the addition of the (*E*)-alkenylcopper **1g** to 2-ethylthio-1-nitro-1-cyclohexene **2b** (entry 11). The Michael addition of the 1,3-dienylcopper reagent<sup>12</sup> **4** to **2a** gives the intermediate nitrotriene **5** 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).<sup>13</sup> The *silica gel catalysis is essential* since the thermic cycloaddition has been shown to be non-stereospecific.<sup>13d</sup>



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).<sup>14</sup>



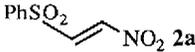
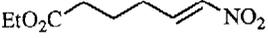
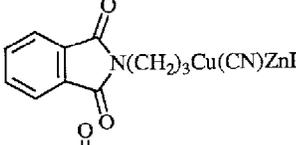
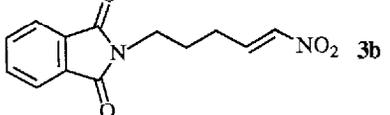
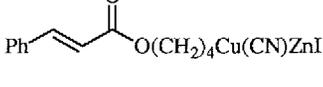
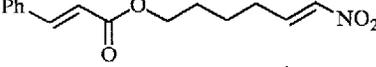
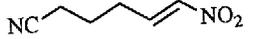
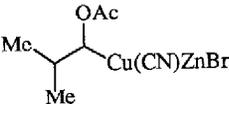
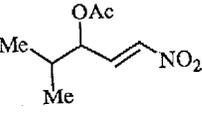
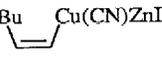
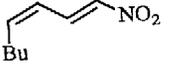
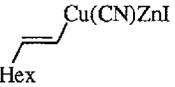
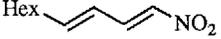
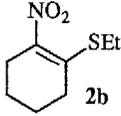
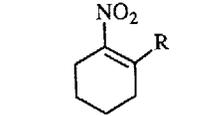
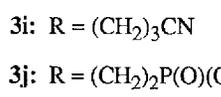
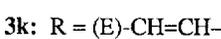
$\beta$ -Disubstituted nitro olefins of type **13**, which can usually not be prepared via a nitro aldol reaction (due to the reversibility of this reaction when ketones are used as substrates), are readily obtained by the reaction of commercially available 2,2-dimethylthio-1-nitroethylene **12** (1 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(CH<sub>2</sub>)<sub>4</sub>Cu(CN)ZnI **1i** which is



available in high yield from 1,4-diiodobutane (zinc dust (2.5 eq.), 40 °C, 2 h), (nitromethylidene)cyclopentane<sup>15</sup> **13d** 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  $\beta$ -alkylthio and  $\beta$ -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 sulfonyl ethylene **2a** or 2-ethylthio-1-nitro-1-cyclohexene **2b** with  $\text{RCu}(\text{CN})\text{ZnX}$ .<sup>a</sup>

Entry	Organocopper reagent	$\beta$ -substituted nitro olefin	Products of Type 3	Yield (%)
1	$\text{EtO}_2\text{C}(\text{CH}_2)_3\text{Cu}(\text{CN})\text{ZnI}$ <b>1a</b>			79
2	 <b>1b</b>	<b>2a</b>		87
3	 <b>1c</b>	<b>2a</b>		82
4	$\text{NC}(\text{CH}_2)_3\text{Cu}(\text{CN})\text{ZnI}$ <b>1d</b>	<b>2a</b>		85
5	 <b>1e</b>	<b>2a</b>		74 <sup>b</sup>
6	 <b>1f</b>	<b>2a</b>		82 <sup>c</sup> (92) <sup>d</sup>
7	 <b>1g</b>	<b>2a</b>		81 <sup>e</sup>
8	<b>1a</b>			89
9	<b>1d</b>	<b>2b</b>		85
10	$(\text{EtO})_2\text{P}(\text{O})(\text{CH}_2)_2\text{Cu}(\text{CN})\text{ZnBr}$ <b>1h</b>	<b>2b</b>		79
11	<b>1g</b>	<b>2b</b>		90 <sup>f</sup>

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

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

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

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

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

<sup>f</sup> Obtained after flash chromatography as the pure (*E*)-isomer.

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6. Besides nitro olefins, several other classes of Michael acceptors having a  $\beta$ -alkylthio or a  $\beta$ -phenylsulfonyl group are known to undergo addition-elimination reactions with nucleophiles, see for example: (a) Dieter, R.K.; Silks, L.A. *J. Org. Chem.* **1983**, *48*, 2786; (b) Dieter, R.K.; Silks, L.A. *J. Org. Chem.* **1986**, *51*, 4687; (c) Dieter, R.K.; Lin, Y.J.; Dieter, J.W. *J. Org. Chem.* **1984**, *49*, 3183; (d) Dieter, R.K.; Fishpaugh, J.R.; Silks, L.A. *Tetrahedron Lett.* **1982**, *23*, 3751; (e) Najera, C.; Yus, M. *Tetrahedron Lett.* **1989**, *30*, 173; (f) Azzena, U.; Cossu, S.; De Lucchi, O.; Melloni, G. *Tetrahedron Lett.* **1989**, *30*, 1845; (g) Riera, A.; Marti, M.; Moyano, A.; Pericas, M.A.; Santamaria, J. *Tetrahedron Lett.* **1990**, *31*, 2173; (h) Schaumann, E.; Fittkau, S. *Synthesis* **1983**, 449; (i) Back, T.G.; Collins, S.; Law, K.-W. *Tetrahedron Lett.* **1984**, *25*, 1689.
7. Typical procedure. (a) Improved preparation of (*E*)-1-nitro-2-phenylsulfonylethylene **2a**. A mixture of (*E*)-1-nitro-2-phenylthioethylene<sup>4a</sup> (9g, 50 mmol) and 50-60% *m*-chloroperbenzoic acid (36 g, 104 mmol; dried as a solution in  $\text{CH}_2\text{Cl}_2$  with  $\text{MgSO}_4$ ) in 600 mL of dry  $\text{CH}_2\text{Cl}_2$  was stirred at 25 °C for 12 h. The reaction mixture was washed successively with water, aq. NaOAc solution and brine, then dried over  $\text{MgSO}_4$ . After evaporation of the solvent, the crude yellow solid was recrystallized from THF/hexane to give 7.77 g (73%) of analytically pure **2a**. (b) Addition of  $\text{RCu}(\text{CN})\text{ZnI}$  to  $\beta$ -sulfonyl nitro olefins. Preparation of 6-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 (3-cyanopropyl)copper derivative **1d** prepared as reported previously.<sup>1,2</sup> The reaction mixture was warmed to -50 °C, quenched after 5 min. with a sat.  $\text{NH}_4\text{Cl}$  solution and worked up as usual. Flash chromatography purification of the resulting crude oil (10:10:1 hexane:dichloromethane:ethyl acetate) gave 710 mg of pure **3d** (85%). In the case of **2b**, the reaction mixture was warmed to 25 °C and stirred 12 h at this temperature.
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9. Retherford, C.; Chou, T.-S.; Schelkun, R.M.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 1833.
10. (*Z*)-1-Iodo-1-hexene (prepared according to Alexakis, A.; Cahiez, G.; Normant, J.F. *Org. Synth.* **1984**, *62*, 1) was converted to (*Z*)-1-lithio-1-hexene (Cahiez, G.; Bernard, D.; Normant, J.F. *Synthesis* **1976**, 245) and treated successively with zinc iodide (1 eq.) in THF/ $\text{Et}_2\text{S}$  (1:1) at -78 °C; after warming to 25 °C, the mixture is added to a solution of a  $\text{CuCN}\cdot 2\text{LiCl}$  (1 equiv.) in THF/ $\text{Et}_2\text{S}$  (1:1) at -78 °C. The use of these conditions is crucial for the formation of a stable vinylic copper reagent. The two following reaction conditions, A:  $\text{CuCN}\cdot 2\text{LiCl}$  (1 eq.) in  $\text{Et}_2\text{S}$ , -78 °C to -30 °C, or B: (i)  $\text{ZnI}_2$  (1 eq.), THF; (ii)  $\text{CuCN}\cdot 2\text{LiCl}$  (1 eq.), THF, are not satisfactory and lead to an extensive dimerization of the alkenylcopper.
11. For an alternative preparation of nitro dienes see: Bloom, A.J.; Mellor, J.M. *Tetrahedron Lett.* **1986**, *27*, 873.
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.* **1955**, *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  $^1\text{H}$  NMR experiments:  $^3\text{J}_{\text{H}1, \text{H}2} = 11.5\text{ Hz}$ ,  $^3\text{J}_{\text{H}2, \text{H}3} = 11.7\text{ Hz}$ ,  $^3\text{J}_{\text{H}3, \text{H}4} = 7\text{ Hz}$ . To confirm the assignment of the relative stereochemistry between  $\text{H}_3$  and  $\text{H}_4$ , **6** was hydrogenated giving  $^3\text{J}_{\text{H}3, \text{H}4} = 5\text{ Hz}$  (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 ethylene and (*E*)-2-ethylthio-1-phenylsulfonylethylene were obtained in a 1:4 ratio (75% yield); (b) the same reaction was performed in the presence of 5 mol % of di-*tert*-butylnitroxide (see: Kornblum, N. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 734) leading to the same product distribution and ruling out a radical mechanism.
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