SYNTHESIS AND REACTIONS OF SUBSTITUTED NITRO-ALLYLATING REAGENTS

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<u>Summary</u> Nitro-cyclohexenylation and α -phenyl-nitro-allylation of nucleophilic centres are achieved (see <u>11-16</u>) with the nitroblyl pivalates <u>2</u> and <u>5</u>, and with the chloride <u>3</u>, which are in turn prepared from the diols <u>9</u> and <u>10</u>, respectively.

We recently reported^{2,3)} that NPP <u>1</u> (2-nitro-3-pivaloyloxy-propene) can be used as a multi-coupling reagent⁴⁾. It reacts selectively with two different nucleophiles Nu¹ and Nu² to give nitro-compounds of type <u>6</u> and <u>7</u> (R=R'=H). The nucleophile Nu¹ can be of very high reactivity (alkyl-, vinyl-, aryllithium)²⁾, of moderate reactivity (lithium ketone or ester enol-





3898

ates)³⁾, as well as of low reactivity (thiols, indoles, secondary amines)^{1,2)} Since the nitro group is amenable to transformation into many other functional groups^{5a)}, the reagent corresponds to the a^2/a^2' -synthon 8, R=R'=H

We now report the synthesis and some reactions of the NPP derivatives and analogues 2, 3, and 5 The original attempts to prepare these compounds were unsuccessful, but they are now available^{5b)} in order (i) to extend the scope of the method, (ii) to see whether the sluggish electrophile nitrocyclohexene⁶⁾ could be activated by a leaving group as present in 2 and 3, and (iii) to obtain information about the mechanism of the nitro-allylation

The 2-nitro-3-pivaloyloxy-cyclohexene $\underline{2}$ is synthesized from the diol⁷⁾ $\underline{9}$ by treatment first with DCC to give $\underline{4}$ which is esterified with pivalic anhydride. The 2-nitro-3-chlorocyclohexene ($\underline{3}$) is obtained from $\underline{4}$ and thionyl chloride. Finally, the open-chain, diastereomerically pure E-2-nitro-1-phenyl-3-pivaloyloxy-propene ($\underline{5}$) is prepared from the readily available⁸⁾ (R*,R*)- or 1-nitrodiol⁹⁾ 10a. It is esterified with pivaloyl chloride to give 10b, from which pivalic acid is smoothly eliminated with sodium acetate. For yields, conditions of preparation, and physical data of 2-5 and 10, and of the products from them, see the accompanying table

Our experience with the three new nitro-allylating reagents 2, 3, and 5 may be summarised as follows. (i) The pivaloyloxy-nitro-cyclohexene 2 reacts well with strong nucleophiles, such as alkyllithiums (see 11), aryllithiums (see 12), and lithio-dithianes (see 13), and also



18

with N-methyl-aniline (\rightarrow 14), while indoles do not add even at 80^oC. (ii) The chloro-nitrocyclohexene 3 on the other hand is not expected to nitro-allylate the above mentioned metal derivatives^{1-3,10} but it furnishes the adduct <u>15</u> with N-methylindole⁶. (iii) Addition of butyllithium to the phenyl-derivative <u>5</u> yields the nitroolefin <u>16</u>, a result compatible with the addition/elimination mechanism proposed earlier^{1-4,11}. (iv) Addition of a second nucleophile or further functionalisations of the products of type <u>6</u> is possible^{1-3,5,12}) Thus, heating of the nitroolefin <u>16</u> with 2,3-dimethylbutadiene produces the *Diels-Alder* adduct <u>17</u> as a 3 2 mixture of two diastereoisomers in high yield Another example of a product arising from multi-coupling is the nitroketone <u>18</u> obtained from <u>16</u> and trimethylsilyloxy-cyclohexene¹³)

<u>Table</u> Compounds <u>2-5</u>, <u>10</u> and products <u>11-18</u> of type <u>6</u> and <u>7</u>

The yields given are those of materials purified by flash-chromatography¹⁴⁾ from 10 mmolar runs Recrystallisation or bulb to bulb distillation furnished analytically pure samples All spectroscopic data are compatible with the structures shown in the *formulae* Melting points, boiling points, as well as the ¹H-NMR shifts (δ [ppm]), coupling constants J[Hz], and multiplicities of the olefinic (o) or single allylic (a) hydrogen(s) are listed

- <u>2</u> m p 22^oC, b p $110^{\circ}C/10^{-5}$ mm, δ_{o} = 7 51, t, J = 4 Hz, δ_{a} = 5.87, m, 95% from <u>4</u> and excess pivalic anhydride, $100^{\circ}C$, 0 75 h, cat amount BF₃ EtOEt.
- <u>3</u> m.p. 23 5^oC; b p 50^oC/10⁻⁵ mm, $\delta_0 = 7$ 36, m; $\delta_a = 5$ 21, br s, 82% from <u>4</u> and excess through chloride in refluxing benzene, 1 h
- $\frac{4}{50}$ $\delta_0 = 7$ 32, t, J = 4 Hz, $\delta_a = 4$ 75, br s, 70% from $\frac{9}{2}$ and 1 1 equiv. dicyclohexylcarbodiimide (DCC) in dioxane, cat amount Cu(I)Cl, 24 h, rt, cf 5b
- 5 mp 69° C; $\delta_0 = 8$ 35, s, $\delta_a = 5$ 18, br s, 95% from <u>10b</u> and dry powdered sodium acetate (1 5 equiv.) in dry ether, 18 h, r t.
- <u>10b</u> m p 69^{0} C, $\delta(\alpha-C_{6}H_{5}) = 6$ 16, d, J = 10 Hz, $\delta(2H,\alpha-0) = 4.19$, d, J = 6 Hz, 95% from <u>10a</u>, excess pivaloyl chloride in refluxing CH₂Cl₂.
- $\frac{11}{cf} b p \frac{68^{\circ}C}{0} \frac{2}{mm}, \delta_{0} = 7 10, t, J = 3 Hz, \frac{92}{s} \text{ from } 2 \text{ and } n-BuL1 \text{ in THF at } -100^{\circ}C \text{ for 1 h,}$
- <u>12</u> m p 58°C, $\delta_0 = 7$ 40, t, J = 4 Hz, 89% from <u>2</u> and bromobenzene, cf ²)
- 13 m p $155^{\circ}C$, $\delta_0 = 7.08$, t, J = 4 Hz, 63% from 2 and phenyldithiane, cf $^{3)}$, -100°C, 3 h, THF
- 14 yellow oil; $\delta_a = 5$ 00, m, 66% from 2 and N-methyl-aniline, 6 d, in THF, 50°C
- <u>15</u> m p 71^oC, $\delta_0 = 7$ 25, t, J = 4 Hz, 47% from <u>3</u> and N-methylindole, 40 h in refluxing benzene
- $\frac{16}{100} \frac{70^{\circ} \text{C}}{10^{-5}} \text{ mm, } \delta_{0}(c_{1S} \text{ to } \text{NO}_{2}) = 6.4, \text{ m, } \delta_{0}(t_{rans}) = 5.5, \text{ br s, } 92\% \text{ from n-BuL1, THF, 1 h, } -100^{\circ} \text{C, cf}^{2}$
- 17 170^oC/O 05 mm, 89% from <u>16</u> and excess refluxing 2,3-dimethyl-1,3-butadiene and a trace hydroquinone, 40 h
- 18 140°C/10⁻⁴ mm, 45% from <u>16</u> and cyclohexanone silyl enolether/SnCl₄/-78°C, 3 l mixture of diastereomers, main isomer ¹H-NMR benzylic CH δ=3 65 (t, 7 Hz), minor isomer ¹H-NMR benzylic CH δ=3 50 (t, 7 Hz), cf ¹³).

- 1) Part of the Ph.D. thesis of P. Knochel, ETH-Zurich (1982).
- 2) P Knochel and D Seebach, Tetrahedron Lett. 22, 3223 (1981)
- 3) P. Knochel and D. Seebach, Nouv. J Chim 5, 75 (1981).
- A multi-coupling reagent ("Verknupfungsreagenz") is a reagent whose reactivity allows the sequential formation of two or more new carbon-carbon bonds.



A,B nucleophiles and (or) electrophiles; FG, FG'. functional groups.

It should have a simple carbon-skeleton, the pattern of which is common to many target molecules. For details and other examples of multi-coupling reagents see¹⁾, full papers are in preparation

- 5) a) Review <u>D</u> Seebach, <u>E W. Colvin</u>, <u>F</u> Lehr, and <u>T. Weller</u>, Chimia <u>33</u>, 1 (1979), b) Improved procedure for the preparation of nitroolefins from nitroaldols see. <u>P</u> Knochel and <u>D</u> Seebach, Synthesis, in print
- 6) Nitrocyclohexene does not react with Li-enolates, with Li-dithianes, or with enamines, which all add smoothly to open chain nitroolefins. (<u>D. Seebach</u>, <u>H F. Leitz</u>, and <u>V Ehrig</u>, Chem. Ber. <u>108</u>, 1924, 1961 (1975), <u>D Seebach</u> and <u>J. Goliński</u>, Helv Chim Acta <u>64</u>, 1413 (1981)), for other nucleophiles see ref ¹² below
- 7) <u>F W. Lichtenthaler</u>, Chem Ber <u>96</u>, 845 (1963); <u>F W Lichtenthaler</u>, <u>T Nakagawa</u>, and A El-Scherbiney, Chem Ber <u>101</u>, 1837 (1968)
- We thank the <u>Boehringer AG</u> (Mannheim) for a generous gift of "dl-threo-l-phenyl-2-nitro--1,3-propanediol" (10a)
- 9) An unambiguous specification of configurations [R*,R* Ξ ℓ (like), R*,S* Ξ μ (unlike)] has just been proposed to prevent the growing confusion in stereochemical nomenclature <u>D Seebach and V Prelog</u>, Angew Chem, review in press
- M Raeber, Diplomarbeit ETH-Zurich (1981)
- 11) If <u>16</u> were formed directly by an S_N2'-process, we would not expect to obtain it in such high yield because <u>16</u> should undergo further reaction in situ.
- 12) E.J Corey and H. Estreicher, J Am Chem Soc 100, 6294 (1978)
- 13) M. Miyashita, T. Yanami, and A. Yoshikoshi, J. Am. Chem. Soc. 98, 4679 (1976)
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