Title
Cycloaddition of tert-Butylcyanoketene to Isocyanides

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 fractions 15-35 mL after the void volume while 4a and 4b were the same solvent. Compounds 5a and 5b were eluted in the yellow fractions 35-80 mL after the void volume. The eluate containing 5a and 5b was concentrated, dissolved in a small volume of 2-bro- methanol (2 mL) and extracted twice with ether. The aqueous phase was concentrated, triturated with 95% EtOH, filtered through Celite, and concentrated, redissolved in 95% EtOH (2 mL), treated with chloroform (2 mL), and filtered. The filtrate was concentrated to afford 100 mg (37% yield) of a reddish solid, a 1:1 mixture of 5a and 5b. LC, TLC, 'H NMR, and 13C NMR revealed no impurities other than a small amount of formate.

cis-1,2,3,4-Tetrahydro-1,2-dimethyl-4,7,8-isoquinolinetriol Hydrochloride (5a). The mixture of 5a and 5b (40 mg) was applied to a column of C-18 Porasil B (37-75 μm, 120 x 0.78 cm) and eluted with 0.01 M KH2PO4 (5.0 mL/min). Compound 5a was eluted between 50 and 100 mL. Ion exchange and EtOH trituration as before afforded 12 mg of 5a as a yellow-brown solid:

'H NMR (D2O) δ 1.71 (3 H, d, J = 6.7, 1-CH3), 3.07 (3 H, s, NCH3), 3.52 (2 H, t, J = 5.7, NCH2), 4.69 (1 H, q, J = 6.7, PhCH), 5.05 (1 H, t, J = 5, CHO), 7.01 (2 H, s, arom); mass spectrum, m/e 194.0857 (100, M-CH3, calc 194.0857), 191 (6), 176 (65), 166 (5), 165 (12).

trans-1,2,3,4-Tetrahydro-1,2-dimethyl-4,7,8-isoquinolinetriol Hydrochloride (5b). Continued elution of the Porasil column afforded 5b in the next 100 mL. Ion exchange and EtOH trituration as before afforded 14 mg of 5b as a yellow-brown solid: 'H NMR (D2O) δ 1.53 (3 H, d, J = 6.9, 1-CH3), 3.05 (3 H, s, NCH3), 3.42 (1 H, dd, J = 1.9, 14, NCH4), 3.82 (1 H, dd, J = 3.5, 14, NCH2), 4.65 (1 H, q, J = 6.9, PhCH), 5.00 (1 H, dd, J = 1.9, 3.7, CHO) 6.98 (2 H, s, arom) for the mass spectrum, see that for 5a.

cis-1,2,3,4-Tetrahydro-6,7-dimethoxy-1,2-dimethyl-4-isoquinolinetriol (6a). Compound 4a (35 mg, 0.14 mmol) in methanol (2 mL) was treated with ethereal diazomethane (3 mL, 0.25 M, 0.75 mmol, 500 mol%). After 5 h, the solvent was evaporated, methanol (2 mL) was added, and the pH was adjusted to 1-2 with conc HCl. More diazomethane (2 mL, 330 mol%) was added, and after 18 h the sample was concentrated, dissolved in water and saturated sodium carbonate, extracted into chloroform, and dried over magnesium sulfate. Evaporation of the solvent afforded 20 mg (50% yield) of 5a. TLC (cyclohexane-chloroform-diethylamine, 50:40:10) Rf 0.18 (lit. Rf 0.48). The 1H NMR was consistent with the literature.

trans-1,2,3,4-Tetrahydro-6,7-dimethoxy-1,2-dimethyl-4-isoquinolinetriol (6b) was prepared from 4b according to the above procedure; TLC Rf 0.15 (lit. Rf 0.39). The 1H NMR was consistent with literature.

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Registry No. 1, 51-43-4; 2, 79254-31-2; 2-HCl, 79254-32-3; 3, 79201-21-1: 3-HCl, 79201-22-2; 4a, 79201-23-3; 4a-HCl, 79201-24-4; 4b, 79201-25-5; 4b-HCl, 79201-26-6; 5a, 79201-27-7; 5a-HCl, 79201-28-8; 5b, 79201-29-9; 5b-HCl, 79201-30-0; 6a, 79254-33-4; 6b, 79254-34-5; formaldehyde, 50-00-0; acetaldehyde, 75-07-0.

Cycloaddition of tert-Butylcyanoketene to Isocyanides

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The reaction of tert-butylnacyanoketene with a series of isocyanides results in an unusual mode of addition involving the carbonyl bond of the ketene. The scope and mechanism of these cycloadditions are discussed.

Reported here is a study of the cycloaddition of tert-butylnacyanoketene (TBCK) to isocyanides, a reaction which proceeds anomalously when compared to other ketene/isocyanide additions. Specifically, it is shown that 2 mol of the ketene react with 1 mol of isocyanide to give good yields of the previously unobserved imino lactones 5a-e. Such products result from a reaction mode in which the cycloaddition takes place across the carbonyl bond of the ketene components. This is unusual since all other reported examples of ketene/isocyanide cycloadditions give products arising from reactions involving addition to the alkene bond of the cumulene. For example, the 1-imino-2,4-cyclopentanedione (1) was obtained in 90% yield when benzyl isocyanide was treated with diphenylketene at 20 °C.1

The cycloadditions reported here were accomplished by the addition of a benzene solution of TBCK2 to a slight excess of the isocyanides at ambient temperature. The reactions were complete within a few minutes and the products isolated by standard methods. Although the yields differed slightly, the same products were obtained when the mode of addition was reversed or if the temperature of the reaction was maintained at -20 °C. In one case, the ketene was slowly added to an excess of neat tert-butylisocyanide in an attempt to obtain products incorporating more than 1 equiv of the isocyanide. However,


Table I. Spectral Data

<table>
<thead>
<tr>
<th>compd</th>
<th>yield, %</th>
<th>mp, °C</th>
<th>IR (KBr), cm⁻¹</th>
<th>′H NMR (CDCl₃), δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>97</td>
<td>150-151</td>
<td>2210 (C=N), 1755 (C=N), 1675, 1640 (C=C)</td>
<td>1.45 (s), 1.4 (s), 1.33 (s)</td>
</tr>
<tr>
<td>5b</td>
<td>73</td>
<td>189-190</td>
<td>2210 (C=N), 1755 (C=N), 1670, 1635 (C=C)</td>
<td>7.7-7.0 (m, 5 H), 4.85 (s, 2 H), 1.4 (s, 9 H), 1.3 (s, 9 H)</td>
</tr>
<tr>
<td>5c</td>
<td>70</td>
<td>82-83</td>
<td>2210 (C=N), 1750 (C=N), 1675, 1640 (C=C)</td>
<td>3.9-3.5 (m, 2 H), 2.0-0.7 (m, 25 H), 1.4 (s), 1.3 (s)</td>
</tr>
<tr>
<td>5d</td>
<td>82</td>
<td>146-147</td>
<td>2210 (C=N), 1745 (C=N), 1675, 1640 (C=C)</td>
<td>4.0-3.5 (br, 1 H, CH₃), 2.0-1.0 (m, 28 H), 1.4 (s), 1.3 (s)</td>
</tr>
<tr>
<td>5e</td>
<td>89</td>
<td>201-202</td>
<td>2210 (C=N), 1745 (C=N), 1675, 1640 (C=C)</td>
<td>7.95-7.35 (4 H), 4.85 (s, 2 H), 2.45 (s, 3 H), 1.4 (s, 9 H), 1.3 (s, 9 H)</td>
</tr>
<tr>
<td>6</td>
<td>82</td>
<td>162-163</td>
<td>2200 (C=N), 1815 (C=O)</td>
<td>1.55 (s), 1.33 (s), 1.28 (s)</td>
</tr>
<tr>
<td>7</td>
<td>95</td>
<td>125-124</td>
<td>3390 (NH), 2220 (C=N), 1780 (C=O), 1630 (exocyclic C=C), 1590 (endocyclic C=C)</td>
<td>8.0-7.6 (br, 1 H), 1.63 (s, 9 H), 1.38 (s, 9 H)</td>
</tr>
<tr>
<td>9</td>
<td>49</td>
<td>119-120</td>
<td>2205 (C=N), 1720 (C=N)</td>
<td>1.53 (s), 1.48 (s), 1.4 (s)</td>
</tr>
</tbody>
</table>

In order to investigate the possibility that 5 represents the kinetic products in these cycloadditions, we also studied the thermal chemistry of 5a. Here it was observed that 5a rearranges to 6 (82%) after 72 h in refluxing benzene. Clearly this must involve equilibration of 5a with

Cycloaddition of tert-Butylcyanoketene

4a. The thermodynamically more stable 6 then results from C-iminolation of the enolate moiety of 4a (Scheme II). A most interesting additional thermolysis pathway was observed when 6 was heated at 145 °C in o-dichlorobenzene for 50 min. Under these conditions, de-tert-butylation occurred to give the butenolide 7 in 95% yield. This is viewed as arising via a retroene reaction as outlined in Scheme II.

Finally, brief mention is made of a comparative study of the cycloaddition of chlorocyanoketene to tert-butyl isocyanide. This ketene, unlike its tert-butyl analogue, readily undergoes self-condensation and thus must be generated in situ. When this was accomplished by the thermolysis of 4-azido-3-chloro-5-methoxy-2(5H)-furanone in refluxing benzene containing an excess of tert-butyl isocyanide, an entirely different reaction course was encountered. Rather than imino lactone, butenolide, or iminocyclopentanedione products, a 3:1 adduct was isolated in 49% yield. The only reasonable structures that can be considered for a 3:1 adduct are 8 or 9, and the latter is favored on the basis of spectral data. The IR spectrum shows a conjugate nitrile absorption at 2205 cm⁻¹ and the imine absorption as a multiplet at δ 1720 cm⁻¹. The ¹H NMR spectrum shows only absorptions for the three tert-butyl groups. The ¹³C NMR spectrum provides significant structural information in that it reveals the required 12 absorptions, and six of these are in the sp² region of the spectrum. Specifically, the absorptions for the tert-butyl groups appear at δ 60.5, 59.9, 56.8, 29.6, 28.8, and 28.7. The remaining sp² carbons appear at δ 157.4, 146.9, 144.0, 135.9, 114.6, and 87.1.

This adduct is presumably favored over the previously described examples since, under the conditions utilized, the ketene would be in very low concentration relative to that of the isocyanide. Thus, the initially formed zwitterion analogous to 3 reacts further with additional isocyanide rather than ketene. In any regard, the synthesis of analogues of 9 by this method appears limited in scope since complex product mixtures were obtained when chlorocyanoketene was generated in the presence of less bulky isocyanides, e.g., benzyl and (p-tolylsulfonyl)methyl isocyanide.

Experimental Section

Reaction of tert-Butylcyanoketene with tert-Butyl Isocyanide. A solution of 6 mmol of tert-butyl cyanoketene was prepared by refluxing 0.906 g (3 mmol) of 2,5-diazido-3,6-di-tert-butyl-1,4-benzoquinone in 25 mL of anhydrous benzene for 75 min. The benzene solution was cooled to room temperature and then was added dropwise to 2.106 g (18 mmol) of benzyl isocyanide. The reaction mixture was stirred for 1 day. The volatile components were removed in vacuo, and the crude reaction residue was chromatographed on silica gel to give 0.797 g (73%) of compound 5b. Recrystallization from hexane-chloroform provided the analytical sample: mp 189-190 °C; mass spectrum (CI), m/e (relative intensity) 364 (M + 1, 15), 241 (16), 214 (8), 180 (12), 157 (12), 124 (100), 92 (6), 91 (48). Anal. Caled for C₁₄H₁₃N₃O₂: C, 69.30; H, 6.21. Found: C, 69.17; H, 6.20.

Reaction of tert-Butylcyanoketene with Benzyl Isocyanide. A solution of 6 mmol of tert-butyl cyanoketene was prepared by refluxing 0.906 g (3 mmol) of 2,5-diazido-3,6-di-tert-butyl-1,4-benzoquinone in 25 mL of anhydrous benzene for 75 min. The benzene solution was cooled to room temperature and then was added dropwise to 2.106 g (18 mmol) of benzyl isocyanide. The reaction mixture was stirred for 1 day. The volatile components were removed in vacuo, and the crude reaction residue was chromatographed on silica gel to give 0.797 g (73%) of compound 5b. Recrystallization from hexane-chloroform provided the analytical sample: mp 189-190 °C; mass spectrum (CI), m/e (relative intensity) 364 (M + 1, 15), 241 (16), 214 (8), 180 (12), 157 (12), 124 (100), 92 (6), 91 (48). Anal. Caled for C₁₄H₁₃N₃O₂: C, 69.30; H, 6.21. Found: C, 69.42; H, 6.43.

Reaction of tert-Butylcyanoketene with Cyclohexyl Isocyanide. By use of the same method, compound 5d was obtained in 70% yield. Recrystallization in hexane gave the analytical sample: mp 82-83 °C; mass spectrum (CI), m/e (relative intensity) 313 (13), 330 (M + 1, 60), 274 (8), 207 (10), 180 (19), 166 (8), 125 (13), 124 (100), 108 (8), 84 (68). Anal. Caled for C₁₄H₁₄N₃O₂: C, 69.30; H, 7.01. Reaction of tert-Butylcyanoketene with tert-Butyl Iso-
cyanide. By use of the above method, compound 5e was obtained in 70% yield. Recrystallization in hexane gave the analytical sample: mp 146-147 °C; mass spectrum (CI), m/e (relative intensity) 356 (M + 1, 6), 125 (8), 124 (100), 110 (22), 84 (10), 83 (32). Anal. Caled for C₁₄H₁₄N₃O₂: C, 70.99; H, 8.17. Found: C, 71.19; H, 8.41.

Reaction of tert-Butylcyanoketene with (p-Tolylsulfonyl)methyl Isocyanide. A solution of 6 mmol of tert-butyl cyanoketene was prepared by refluxing 0.906 g (3 mmol) of 2,5-diazido-3,6-di-tert-benzoquinone in 25 mL of anhydrous benzene for 75 min. The benzene solution was cooled to room temperature and then was added dropwise to a solution of 0.585 g (3 mmol) of (p-tolylsulfonyl)methyl isocyanide in 15 mL of benzene. The reaction mixture was stirred for 1 h. After removal of the solvent, the reaction residue was chromatographed on silica gel to give 1.18 g (89%) of compound 5e. Recrystallization in hexane-chloroform provided the analytical sample: mp 201-202 °C; mass spectrum (CI), m/e (relative intensity) 442 (M + 1, 10), 288 (5), 165 (13), 157 (84), 141 (5), 139 (17), 125 (9), 124 (100). Anal. Caled for C₁₄H₁₃N₃O₂S: C, 62.59; H, 6.12. Found: C, 62.62; H, 6.14.

Thermolysis of Compound 5a. A benzene solution of 0.329 g (1 mmol) of compound 5a in 25 mL of anhydrous benzene was heated at 85 °C under nitrogen for 3 days. After removal of the solvent, the solid material was purified by crystallization from 30 mL of hexane–benzene. This procedure afforded 0.27 g (82%) of the pure compound 6: mp 162-163 °C dec; mass spectrum (CI, m/e (relative intensity) 330 (M + 1, 5), 275 (7), 274 (40), 218 (5), 207 (12), 181 (12), 180 (100), 166 (10), 124 (8); ¹³C NMR (CDCl₃) δ 163.3, 155.2, 140.6, 116.3, 114.6, 104.6, 61.8, 57.4, 51.7, 34.9, 30.3, 29.0, 26.7. Anal. Caled for C₁₄H₁₄N₃O₂: C, 69.30; H, 6.21. Found: C, 69.36; H, 6.45.

Thermolysis of Compound 6. A solution of 0.329 g (1 mmol) of compound 6 in 20 mL of o-dichlorobenzene was heated at 145 °C for 50 min. The solvent was removed in vacuo, and the reaction residue was chromatographed on silica gel. It gave 0.260 (95%) of the product 7. Recrystallization in hexane afforded the analytical sample: mp 123-124 °C; mass spectrum (CI, m/e (relative intensity) 275 (17), 274 (M + 1, 100), 218 (12); ¹³C NMR (CDCl₃) δ 165.2, 154.2, 192.3, 117.6, 114.4, 104.6, 55.7, 36.0, 29.8, 29.3. Anal. Caled for C₁₄H₁₄N₃O₂: C, 65.50; H, 6.56. Found: C, 65.70; H, 6.70. M: 7.20.

Reaction of Chlorocyanoketene with tert-Butyl Isocyanide. A solution of 0.57 g (3 mmol) of 4-azido-3-chloro-5-methoxy-2(5H)-furanone and 0.75 g (9 mmol) of tert-butyl isocyanide in 10 mL of anhydrous benzene was well stirred under nitrogen at 80 °C for 1 day. After removal of the volatile components in vacuo, the reaction residue was chromatographed on
Fluorine compounds are widely used as drugs in pharmacology and chemotherapy. However, a convenient synthetic route to α,β-fluoro amines, particularly those with a primary amine function, does not exist. These compounds exhibit biological activity on the central nervous system. A new synthetic route to fluoro amines has recently been reported by Kollonitsch and co-workers. This method, however, needs special handling of sulfur tetrafluoride, a very toxic reagent. More frequently used is a,β-chlorofluoro compounds should be mentioned.

Fluorine compounds are widely used as drugs in pharmacology and chemotherapy. However, a convenient synthetic route to α,β-fluoro amines, particularly those with a primary amine function, does not exist. These compounds exhibit biological activity on the central nervous system. A new synthetic route to fluoro amines has recently been reported by Kollonitsch and co-workers. This method, however, needs special handling of sulfur tetrafluoride, a very toxic reagent. More frequently used fluorinating reagents are fluoroalkylamines, metallic and nonmetallic fluorides, trifluoromethyl hypofluorite. Fluorodesulfurization and diazotization reactions have also been carried out in this connection. Finally, the possible replacement of the chlorine atom by an amine function in α,β-chlorofluoro compounds should be mentioned.

The fact that the hydrogen fluoride addition to epoxides is a very clean and good method for preparing α,β-fluoro alcohols led us to investigate the same type of reaction sequence (eq 1) with secondary aziridines. This reaction has been performed in the mytomycine series. Numerous synthetic methods leading to secondary aziridines have been developed during the past 15 years, and these compounds in monocyclic, steroid, and acyclic series are now easily available.

Prompted by a recent paper of Wade concerning the synthesis of fluoro amines via aziridine ring opening by HF-pyridine (Olah's reagent), which appeared while this work was in progress, we present results obtained in our laboratory. In preliminary notes we have reported the synthesis of α,β-fluoro amines by ring-opening of secondary or N-activated aziridines with anhydrous hydrogen fluoride, Olah's reagent, or modified Olah's reagent. We present here a comparative study of the fluorinating ability of these three reagents toward aziridines. The stereoselectivity of the reaction appears to be very different in each case, and the synthetic advantages of each reagent are discussed.

Results

Two fluorinating agents were previously used with secondary aziridines (R = H), i.e., anhydrous hydrogen fluoride and Olah's reagent. Fluoro amines are generally obtained in fair yields (Table I). However, in some cases we could not get satisfactory results (i.e., 10aT and 10aA, 10aB and 10aC, 10aD and 10aE).

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