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CYANOKETENES. SYNTHESIS AND CYCLOADDITIONS TO FORMIMIDATES

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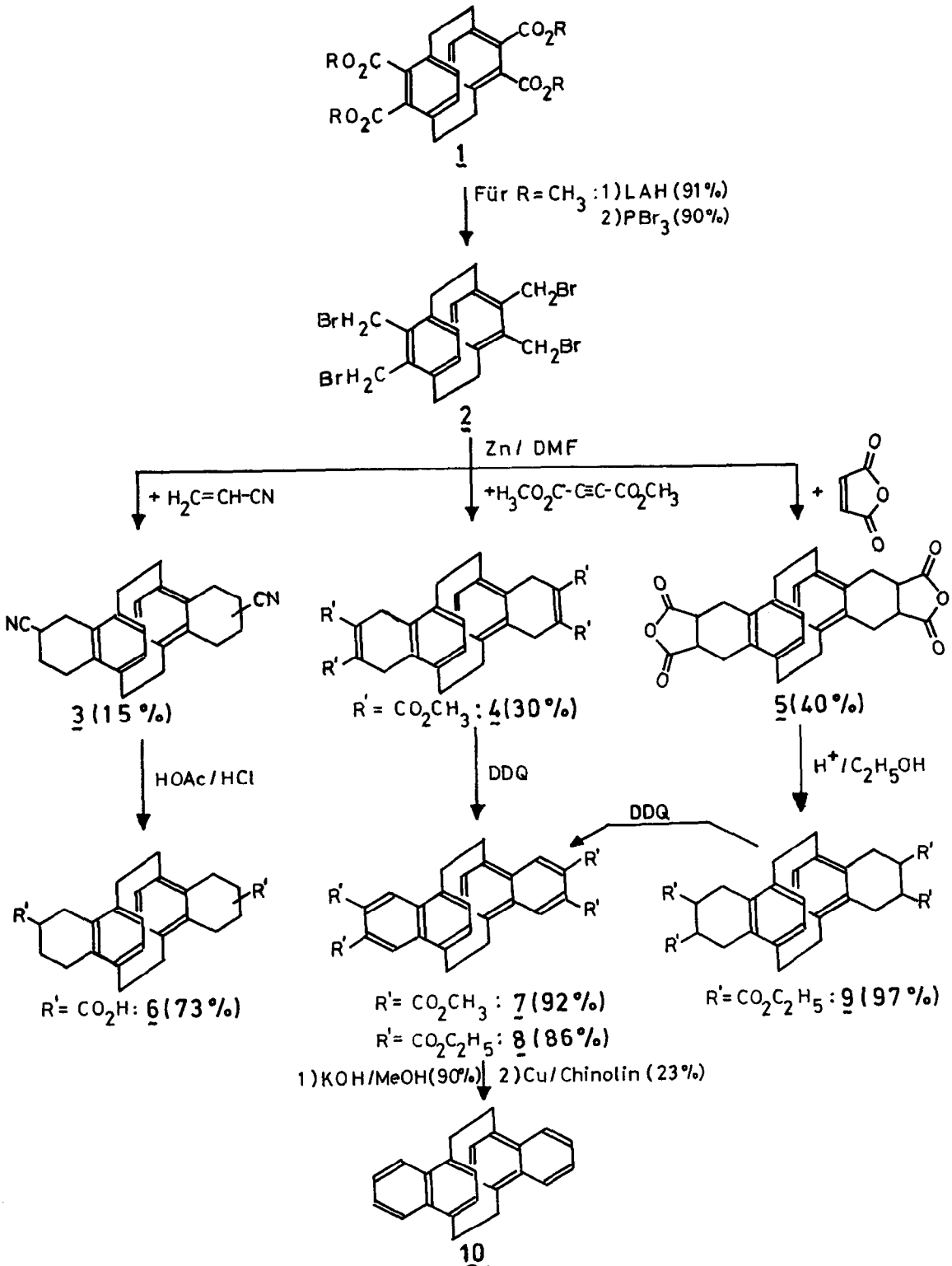
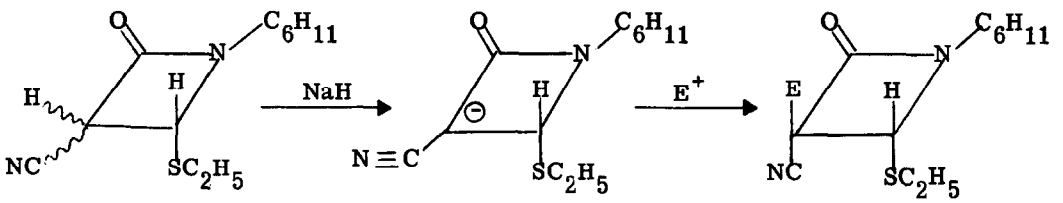
We have previously reported that β-azido-α-chloro-γ-methoxy-$\Delta^{\alpha,\beta}$-crotonolactone (1a) undergoes thermolysis in refluxing benzene to give chlorocyanoketene (2a) and methylformate.[1] Reported here is the observation that the corresponding α-bromo- and α-iodo-analogs of 1 undergo analogous thermolyses to give the respective halocyanoketenes, 2b and 2c. In addition, it is reported that these halocyanoketenes, 2a-c, as well as tert-butyl-, 2d, and methylcyanoketene, 2e,[2] readily undergo stereospecific cycloadditions to a variety of formimidates to give 2-azetidinones (β-lactams), 4a-z.

The β-azido-α-halo-γ-methoxy-$\Delta^{\alpha,\beta}$-crotonolactones, 1b,c, were prepared in high yields from the corresponding mucohalic acids[3] by the general procedure previously reported for the synthesis of 1a.[1] These azidobutenolides along with the appropriately substituted 2,5-diazido-1,4-benzoquinones,[2] e.g., 2,5-diazido-3,6-dimethyl-, 3e and 2,5-diazido-3,6-di-tert-butyl-1,4-benzoquinone, 3d, provide the best known precursors to a variety of substituted cyanoketenes. In view of the renewed interest in the synthesis and biological activity of monocyclic β-lactams, a detailed study of the cycloadditions of chloro-, bromo-, iodo-, methyl-, and tert-butylcyanoketene to formimidates was accomplished. The salient result of this study is the observation that these cyanoketenes undergo stereospecific cycloaddition to a wide variety of formimidates and thioformimidates to give 2-azetidinones in which the 3-cyano and the 4-protio groups reside in a trans arrangement, i.e., 4a-z. In addition, 4d was used as a model and converted to the anion, 6, which reacts stereospecifically with a variety of electrophiles to give 2-azetidinones having further elaboration at position -3, i.e., 7a-i.

For the halocyanoketenes, the cycloadditions were accomplished by refluxing a solution containing 1.0 equivalent of the β-azido-α-halo-$\Delta^{\alpha,\beta}$-butenolides, 1a-c, and 1.1 equivalents of the appropriate formimidate for several hours. For the alkylcyanoketenes, 3d,e, a benzene and chlorobenzene solution, respectively, containing 0.5 equivalents of the 2,5-diazidoquinone was slowly added to a refluxing benzene solution containing 1.1 equivalents of the formimidate. After an additional hour the solvent was removed in vacuo and the product purified by chromatography or recrystallization. The yields reported for the 2-azetidinones, 4a-z, are those obtained for the puri-


RO2C
CO2R
RO2C
CO2R
1
Für R = CH3 : 1) LAH (91%)
2) PBr3 (90%)
BrH2C
CH2Br
BrH2C
CH2Br
2
Zn / DMF
+ H2C=CH-CN
+ H3CO2C-C≡C-CO2CH3
+
NC
CN
3 (15 %)
R'= CO2CH3 : 4 (30 %)
5 (40 %)
HOAc / HCl
DDQ
H+ / C2H5OH
DDQ
R'= CO2H : 6 (73 %)
R'= CO2CH3 : 7 (92 %)
R'= CO2C2H5 : 8 (86 %)
R'= CO2C2H5 : 9 (97 %)
1) KOH / MeOH (90%) 2) Cu / Chinolin (23 %)
10

route and allow the construction of still further examples of potentially active β-lactams. To this end, an investigation to further elaborate the cyano-β-lactam ring system was initiated. Specifically, we envisaged that anions such as 6 would function as powerful synthetic precursors to a wide variety of substituted 2-azetidinone derivatives. We now report that this anion, 6, can be generated in greater than 85% yield by an initial reductive dechlorination (Zn/CH_3CO_2H) of 4d to give the dihydro derivative 5,[4] which upon treatment with NaH/THF at 0° gives the anion 6. Significantly, this anion undergoes stereospecific alkylation, acylation, aldol condensation and Michael addition, and representative examples are given below. Again, only one isomer was detected,[5] and it is assumed that these arise via attack of the electrophile from the side opposite the $-SCH_2CH_3$ group. This is, in fact, certainly true for the alkylation with methyl iodide since the product is identical to that formed when methylcyanoketene cycloadds to N-cyclohexyl-S-ethylthioformimidate, and the stereochemistry of this adduct has been established (see following manuscript).



5 6 7

	E^+	E	Yield	mp
a)	CH_3I	CH_3-	91	oil
b)	$CH_2=CH-CH_2Br$	$CH_2=CH-CH_2-$	59	oil
c)	CH_3COCl	CH_3CO-	29	oil
d)	C_6H_5COCl	C_6H_5CO-	43	oil
e)	CH_3OCOCl	CH_3OCO-	90	65-66°
f)	C_6H_5CHO	$C_6H_5-\underset{OH}{CH}-$	60	127-129°
g)	$(CH_3)_3-C-N{=}{=}O$	$(CH_3)_3-C-NH-CO-$	72	63-65°
h)	$CH_2=CH-CN$	$NC-CH_2CH_2-$	63	41-42°
i)	$CH_2=CH-COCH_3$	$CH_3CO-CH_2-CH_2-$	92	oil

In conclusion, we wish to emphasize that the cyanoketene cycloadditions and β-lactam anion chemistry reported here, in conjunction with our previously related report that β-azidopyrrolinones ring contract to β-lactams,[1] constitutes perhaps the best synthetic route to highly substituted monocyclic 2-azetidinones.

References and Notes

1. H. W. Moore, L. Hernandez, Jr. and A. Sing, J. Am. Chem. Soc., 98, 3728 (1976).
2. W. Weyler, W. Duncan, and H. W. Moore, ibid., 97, 6187 (1975).
3. Mucobromic acid is commercially available, while β-chloro-α-iodo-γ-hydroxy-$\Delta^{\alpha,\beta}$-crotonolactone was prepared by the method of E. Beška and P. Rapoš, J. Chem. Soc., Perkin I, 2470 (1976). The spectral and analytical properties of all new compounds reported here are in agreement with their indicated formulations.
4. The β-lactam, 5, thus formed was obtained as a mixture of the cis and trans isomers in a ratio of 2 : 1, respectively. The stereochemistry was readily assigned on the basis of the coupling constants for the methine protons. See, K. D. Banrow and T. M. Spotswood, Tetrahedron Lett., 3325 (1965).
5. Actually two diastereomers were observed from the aldol product 7f. However, these are due to the difference in chirality at the carbinol carbon.
6. The authors wish to thank the National Science Foundation (CHE-06932) for financial support.