1,3-Dipolar cycloaddition reactions of Munchnone and Sydnone derivatives obtained from 4,5,6,7-tetrahydrothieno(3,2-c)pyridine-4 and -6 carboxylic acids.

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Abstract - The 1,3-dipolar cycloaddition of dimethyl acetylenedicarboxylate with mesoionic munchnones and sydnones derived from 4,5,6,7-tetrahydrothieno(3,2-c)pyridine-4 and -6 carboxylic acids afforded respectively new ring-fused pyrroles and pyrazoles.

The conversion of secondary amino acids into pyrroles via intermediate mesoionic 1,3-oxazolium-5-olates (munchnones)[1] has been utilized in converting the "cyclic" amino acids, tetrahydro-β-carboline-1 and -3 carboxylic acids[2] and tetrahydroisoquinoline-1[3] and -3[4] carboxylic acids into novel ring-fused pyrroles. These reactions involved a 1,3-dipolar cycloaddition of the munchnone,behaving like a cyclic azomethine ylide[5], to the corresponding acetylenic or olefinic dipolarophile followed by CO$_2$ evolution, and aromatization or tautomerization.

The present paper deals with the application of the above reaction on two other types of cyclic amino acid ring systems, namely 4,5,6,7-tetrahydrothieno(3,2-c)pyridine-4 and -6 carboxylic acids. Moreover it will describe the synthesis of fused-pyrazoles by a similar reaction with the corresponding 1,2,3-oxadiazolium-5 olates (sydnones)[2].

The amino-acid 4 was prepared[6] by Pictet-Spengler cyclisation with formaldehyde of (±)-β-(2-thienyl) alanine 1 or by hydrogenolysis of compound 3[6] with stannous chloride-hydrochloric acid in acetic acid.

The amino acid 12 (F > 260°) was easily obtained by condensation of 2-(2-thienyl)ethyl amine with glyoxylic acid, in water, at room temperature. The conversion of 4 into the 5,9-dihydro-thieno(3,2-f)indolizine 7, involved treatment with dimethyl acetylenedicarboxylate in acetic anhydride. No attempt was made to isolate the highly reactive intermediate munchnone 5 and rearrangement of the presumed adduct 6 could be followed by CO$_2$ evolution. But all attempts to convert 12 in the same way were unsuccessful.

The N-nitroso-α-amino-acid 8 (F= 155° (H$_2$O-EtOH)) was cyclodehydrated using acetic anhydride and the resulting sydnone 9 (F= 182° (EtOH)) underwent a 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate in refluxing benzene to give the fused-pyrazole 10 (F= 143° (iPrOH)). Similarly, the crude N-nitroso-derivative 13 (F$_{dec}$ = 145-150°) was transformed into 15 (F= 80° (iPrOH-iPr$_2$O)) via the syndnone 14 (F= 165° (iPrOH)).

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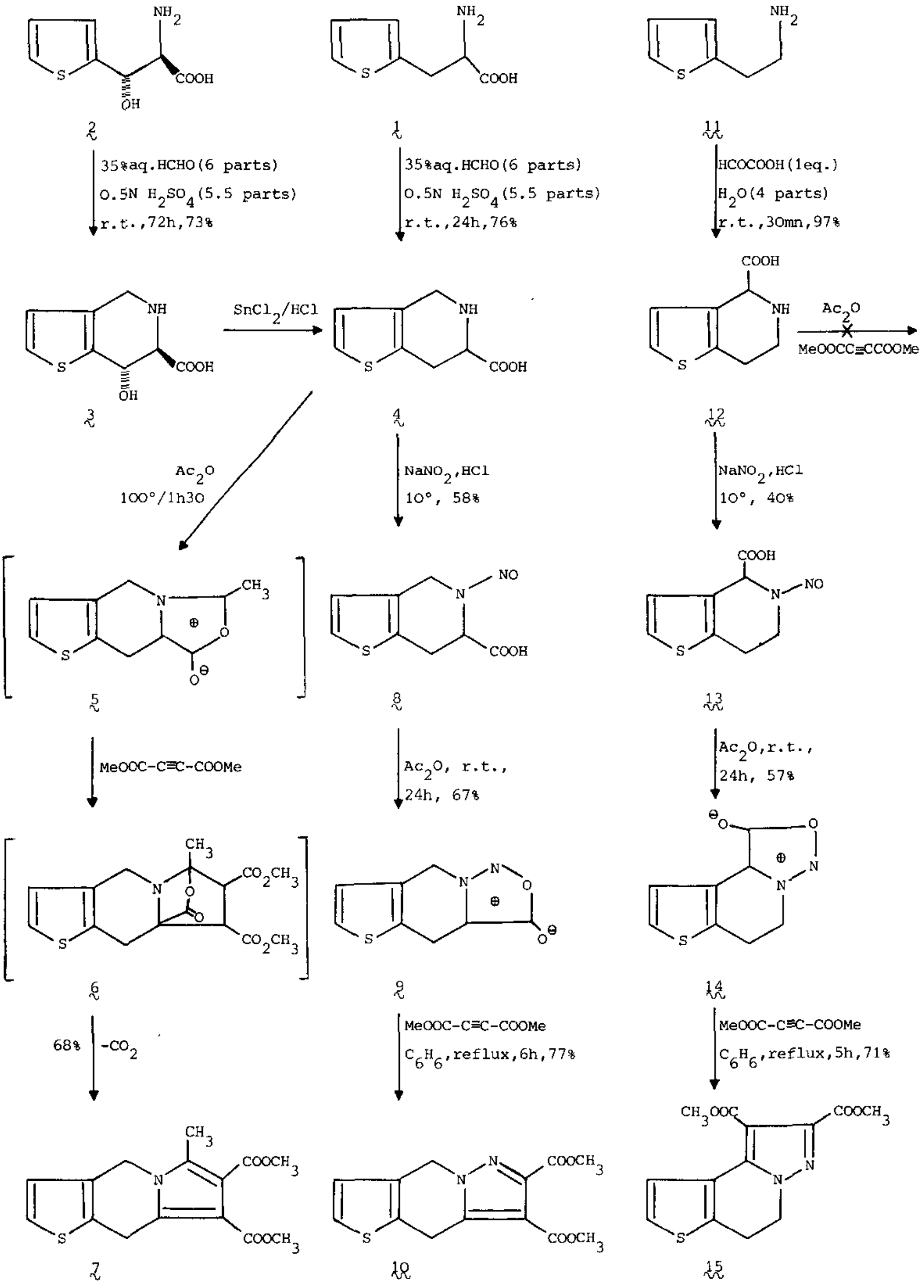
NH2
COOH
OH
2
1
11
35%aq.HCHO(6 parts)
0.5N H2SO4(5.5 parts)
r.t.,72h,73%
35%aq.HCHO(6 parts)
0.5N H2SO4(5.5 parts)
r.t.,24h,76%
HCOCOOH(1eq.)
H2O(4 parts)
r.t.,30mn,97%
NH
SnCl2/HCl
Ac2O
MeOOCC≡CCOOMe
3
4
12
Ac2O
100°/1h30
NaNO2,HCl
10°, 58%
NaNO2,HCl
10°, 40%
CH3
NO
5
8
13
MeOOC-C≡C-COOMe
Ac2O, r.t.,
24h, 67%
Ac2O,r.t.,
24h, 57%
CO2CH3
6
9
14
68%
-CO2
MeOOC-C≡C-COOMe
C6H6,reflux,6h,77%
MeOOC-C≡C-COOMe
C6H6,reflux,5h,71%
COOCH3
CH3OOC
7
10
15

N°	IR $\nu(cm^{-1})$	^{1}H. N.M.R. δ(ppm) , J (Hz)
7	ν_{CO}:1725,1700	(CDCl$_3$) : 2,35(s,3H); 3,75(s,3H); 3,77(s,3H); 4,18(t,2H,J=3); 4,78(t,2H,J=3); 6,78 , 7,18(2d,2H,J=5,5)
8	ν_{CO}:1710	(DMSO d$_6$) : 4,27 , 5,17(2d,2H); 6,07(q,1H); 6,88 , 7,37 (2d,2H,J=5,5)
9	ν_{CO} :1730	(DMSO d$_6$) : 3,87(t,2H,J=4) ; 5,50(t,2H,J=4) ; 6,95 , 7,48(2d,2H,J=5,5)
10	ν_{CO}:1745,1702	(CDCl$_3$) : 3,84(s,3H) ; 3,88(s,3H); 4,30(t,2H,J=4,0) ; 5,23(t,2H,J=4) ; 6,83 , 7,25(2d,2H,J=5,5)
12	ν_{COO^-}:1555,1625	(CF$_3$COOH) : 3,25(s*,2H); 3,85(s*,2H); 5,50(s*,1H) ; 7,15 , 7,33(2d,2H,J=5,5)
13	ν_{CO} :1730	(DMSO d$_6$) : 4,21(m,1H); 4,93(m,1H); 5,82(s,1H); 6,98 , 7,30(2d,2H,J=5,5)
14	ν_{CO} :1740,1755	(DMSO d$_6$) : 3,37(t,2H,J=7,5); 4,67(t,2H,J=7,5); 7,12 , 7,43(2d,2H,J=5,5)
15	ν_{CO}:1705	(CDCl$_3$) : 3,28(t,2H,J=7,5); 3,92(s,3H); 3,97(s,3H); 4,45(t,2H,J=7,5); 7,25 , 7,73(2d,2H,J=5,5)

s* : broadened singlet

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