SYNTHESIS OF THIENO[3,2-c]- AND THIENO[2,3-c]PYRID-3-ONES

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Abstract — The Friedel-Crafts cyclization of N-(3-thenyl)- and 
N-(2-thenyl)-glycine derivatives is described. The method leads to an 
alternative synthesis of 1,2,3,4-tetrahydro-N-[(2-chlorophenyl)methyl]-
thieno[3,2-c]pyridine(ticlopidine(6d)).

The title compounds have not been synthesized from glycine derivatives under conditions of the 
Friedel-Crafts reaction(Scheme 1). We have 
failed in cyclization of diaralkylglycyl chloride 
in the presence of stannic chloride at 5°C in 
benzene, forming N,N-diaralkylmethyleneammonium 
salt1 with the loss of carbon monoxide.2

We have now succeeded in the synthesis of 
1,2,3,4-tetrahydrothieno[3,2-c]- and [2,3-c]pyrid-
3-one derivatives(5a-d and 13a) from N,N-disubstituted glycines(3a-d, 11a). We also have 
applied this cyclization reaction to the synthesis of ticlopidine(6d), which is one of new potent 
blood platelet anti-aggregation agents.3,4

The synthetic routes and conditions leading to tetrahydrothieno[3,2-c]pyrid-3-ones(5a-d) are 
shown in Scheme 2 and Table 1. N-Tosyl- and N-methanesulfonyl-N-(3-thenyl)glycine ethyl esters 
(3a,b), derived from the corresponding ester(2), were hydrolized to glycines(4a,b). Obtained 4a,b 
were treated with oxalyl chloride in benzene at 50°C, and, subsequently, in situ with stannic 
chloride(1.1 molar equiv.) at 5°C. The usual work up after continuous stirring overnight at room 
temperature gave 1,2,3,4-tetrahydro-N-tosyl- and N-methanesulfonylthieno[3,2-c]pyrid-3-ones(5a 
and 5b) in 64% and 72% yields, respectively.

On the other hand, N-benzyl-N-(3-thenyl)glycine(4c) under the same conditions gave diaralkyl-
amine(8c) and N,N,N,N-tetralkylmethyleneamine(7c), which resulted from decarbonylation 
reaction, instead of cyclized products such as 5c. Thienopyridine 5c was obtained by treatment 
of the ester 3c or the hydrochloride of 4c with 80%-sulfuric acid, which has been successfully
Table 1. Reaction conditions and yields for Scheme 2.

<table>
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<tr>
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<th>ii</th>
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<tbody>
<tr>
<td>a</td>
<td>TsCl/pyridine 93%</td>
<td>aq. KOH/tBuOH 78%</td>
<td>1) (COCl)₂ 2) SnCl₄ 64%</td>
<td></td>
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<tr>
<td>b</td>
<td>MeSO₂Cl/TEA 93%</td>
<td>aq. KOH/tBuOH 81%</td>
<td>1) (COCl)₂ 2) SnCl₄ 72%</td>
<td></td>
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<tr>
<td>c</td>
<td>PhCH₂Cl/K₂CO₃ 79%</td>
<td>6N-HCl 75%</td>
<td>80%-H₂SO₄ 85%</td>
<td>80%-H₂SO₄ 60%</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>2-Cl-C₆H₄CH₂Cl/ K₂CO₃ 84%</td>
<td>6N-HCl 91%</td>
<td>80%-H₂SO₄ 63%</td>
<td>80%-H₂SO₄ 58%</td>
<td>LiAlH₄-AlCl₃ 63%</td>
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used as a catalyst for the similar cyclization reaction in the isoquinolone synthesis by G. Grethe et al., in 60% or 58% yield, respectively.

The same reaction sequences starting from 2-thenyl chloride as shown in Scheme 3 were also studied. The cyclized product, 1,2,3,4-tetrahydro-N-tosylthieno[2,3-c]pyrid-3-one (13a) was yielded in 23%, by interaction of the N-tosyl-N-(2-thenyl)glycine (12a) with stannic chloride. On the contrary, N-benzyl-N-(2-thenyl)glycine derivative did not give any cyclized product when heated in various concentrations of sulfuric acid.

Thienopyridinone 5d was obtained from N-[(2-chlorophenyl)methyl]-N-(3-thenyl)glycine ethyl ester (9d), which was prepared from 3-thenyl bromide (1) and N-[(2-chlorophenyl)methyl]glycine ethyl ester in ethanol in the presence of anhydrous K₂CO₃ in a yield of 45% from 1. Reduction of 5d with LiAlH₄—AlCl₃ in boiling THF provided ticlopidine (6d) in 63% yield. The present scheme appears to be a fairly practical route for the synthesis of 5d because of giving no side products in each step. Physical properties of cyclized compounds are listed in Table 2.

Table 2. Physical properties of thieno compounds

<table>
<thead>
<tr>
<th>mp or bp(°C)</th>
<th>ν(C=O)</th>
<th>¹H-NMR (ppm)</th>
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<tbody>
<tr>
<td>5a 182-183</td>
<td>1662 cm⁻¹</td>
<td>(CDCl₃): 2.22(s,3H), 3.85(s,2H), 4.39(s,2H) 6.7-7.6(aromatic 6H)</td>
</tr>
<tr>
<td>5b 123-123.5</td>
<td>1660 cm⁻¹</td>
<td>(CDCl₃): 2.78(s,3H), 4.15(s,2H), 4.70(s,2H) 7.06(d, J=5.0Hz,1H), 7.80(d, J=5.0Hz,1H)</td>
</tr>
<tr>
<td>5c 134-135 (hydrochloride)</td>
<td>1670 cm⁻¹</td>
<td>(CDCl₃): 3.40(s,2H), 3.76(s,4H), 6.98(d, J=4.6Hz,1H) 7.38(s,5H), 7.70(d, J=4.6Hz,1H)</td>
</tr>
<tr>
<td>5d 129-130 (hydrochloride)</td>
<td>1660 cm⁻¹</td>
<td>(CDCl₃): 3.46(s,2H), 3.91(s,2H), 3.93(s,2H), 6.93(d, J=4.6Hz,1H) 7.3-7.6(m,4H), 7.66(d, J=4.6Hz,1H)</td>
</tr>
<tr>
<td>12a 170-171</td>
<td>1670 cm⁻¹</td>
<td>(CDCl₃): 2.33(s,3H), 4.00(s,2H), 4.73(s,2H) 7.1-7.4(aromatic 6H)</td>
</tr>
<tr>
<td>6d 117-120 (0.5mmHg)</td>
<td>—</td>
<td>(CDCl₃): 2.85(s,4H), 3.60(s,2H), 3.76(s,2H), 6.64(d, J=4.6Hz,1H) 7.03(d, J=4.6Hz,1H), 7.1-7.7(m,4H)</td>
</tr>
</tbody>
</table>
REFERENCES AND NOTES

4) J. P. Maffrand and R. Boigegrain, Heterocycles, 1979, 12, 1479.
7) All new compounds in this paper gave satisfactory elemental analyses.

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