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

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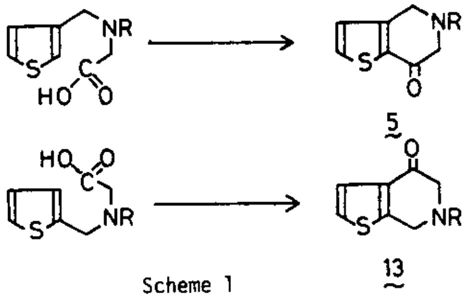
Abstract —— The Friedel-Crafts cyclization of N-(3-thenyl)- and N-(2-thenyl)-glycine derivatives is described. The method leads to an alternative synthesis of 1,2,3,4-tetrahydro-N-[(2-chlorophenyl)methyl]-thieno[3,2-c]pyridine(ticlopidine)(6d).

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 salt[1] with the loss of carbon monoxide.[2]

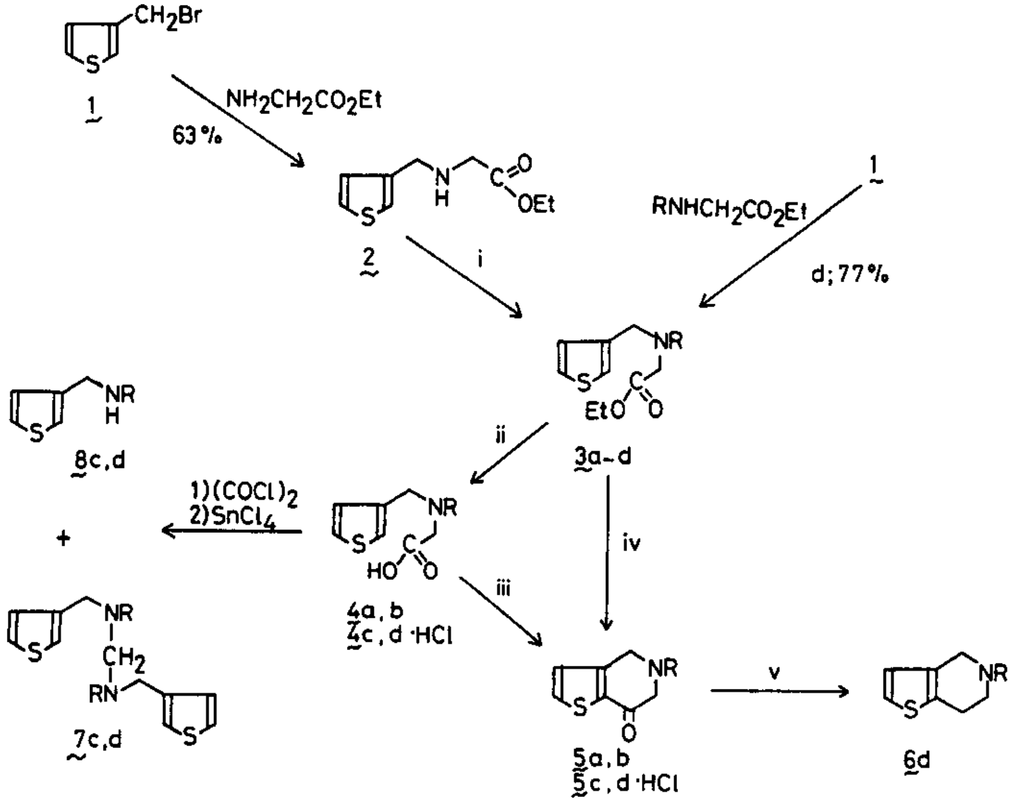


Scheme 1

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 diaralkylamine(8c) and N,N,N,N-tetralalkylmethylenediamine(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



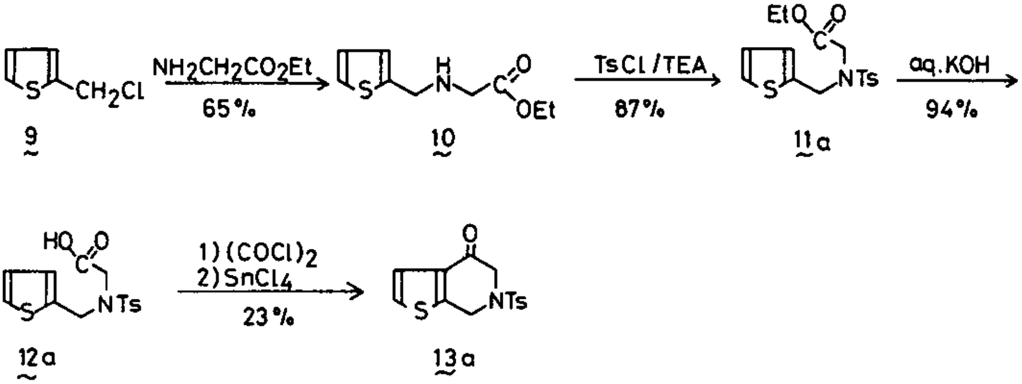
Scheme 2

Table 1. Reaction conditions and yields for Scheme 2.

	i	ii	iii	iv	v
a	TsCl/pyridine 93%	aq.KOH/tBuOH 78%	1) $(COCl)_2$ 2) $SnCl_4$ 64%	———	———
b	$MeSO_2Cl$/TEA 93%	aq.KOH/tBuOH 81%	1) $(COCl)_2$ 2) $SnCl_4$ 72%	———	———
c	$PhCH_2Cl/K_2CO_3$ 79%	6N-HCl 75%	80%-H_2SO_4 85%	80%-H_2SO_4 60%	———
d	2-Cl-$C_6H_4CH_2Cl$/ K_2CO_3 84%	6N-HCl 91%	80%-H_2SO_4 63%	80%-H_2SO_4 58%	$LiAlH_4$-$AlCl_3$ 63%

used as a catalyst for the similar cyclization reaction in the isoquinolone synthesis by G.Grethe et al.[5], 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.



Scheme 3

Thienopyridinone 5d was obtained from N-[(2-chlorophenyl)methyl]-N-(3-thenyl)glycine ethyl ester (3d), which was prepared from 3-thenyl bromide(1) and N-[(2-chlorophenyl)methyl]glycine ethyl ester in ethanol in the presence of anhydrous K_2CO_3 in a yield of 45% from 1. Reduction of 5d with $LiAlH_4$-$AlCl_3$[6] in boiling THF provided ticlopidine(6d) in 63% yield. The present scheme appears to be a fairly practical route for the synthesis of 6d 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

	mp or bp(°C)	ir $\nu_{C=O}$	^{1}H-NMR (ppm)
5a	182-183	1662 cm^{-1}	($CDCl_3$): 2.22(s,3H),3.85(s,2H),4.39(s,2H) 6.7-7.6(aromatic 6H)
5b	123-123.5	1660 cm^{-1}	($CDCl_3$): 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)
5c	134-135 (hydrochloride)	1670 cm^{-1}	($CDCl_3$): 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)
5d	129-130 (hydrochloride)	1660 cm^{-1}	($CDCl_3$): 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)
13a	170-171	1670 cm^{-1}	($CDCl_3$): 2.33(s,3H),4.00(s,2H),4.73(s,2H) 7.1-7.4(aromatic 6H)
6d	117-120 (0.5mmHg)	——	($CDCl_3$): 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)

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7) All new compounds in this paper gave satisfactory elemental analyses.

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