NEW SYNTHESIS OF THIENO[3,2-c]PYRIDINES

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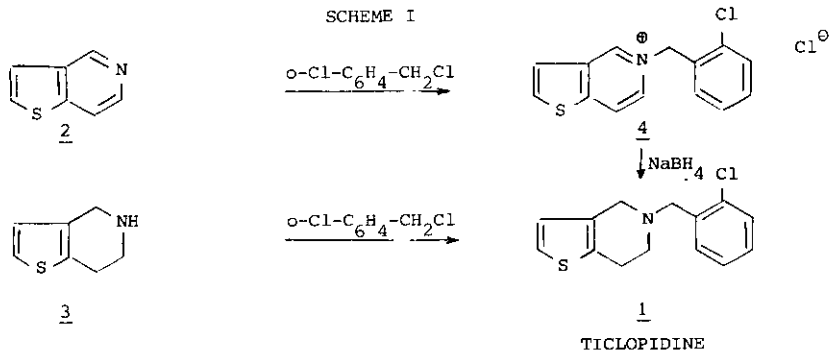
Abstract -A new synthesis of thieno[3,2-c]pyridines by thermal rearrangement of 5-(2-thienyl)oxazolidines is described.

Ticlopidine (1), a new potent blood platelet aggregation inhibitor and antithrombotic agent[1], was synthetized from thieno[3,2-c]pyridine itself (2) or its tetrahydrogenated derivative (3)[2] by the following reactions:

SCHEME I

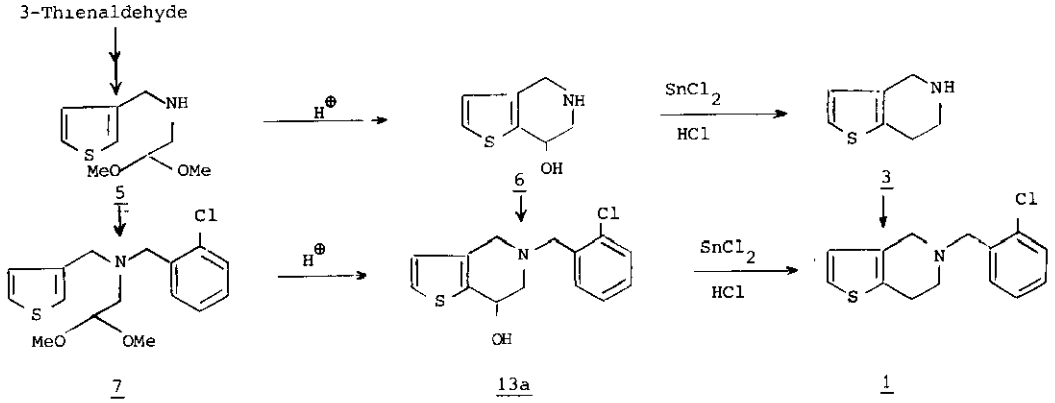


2 → 4 → 1 ; 3 → 1

TICLOPIDINE

An other route to (1)[3] resulted from an application of Bobbitt's[4] improvment of the general Pomeranz-Fritsch isoquinolines synthesis[5] (scheme II).

SCHEME II



5 → 7 ; 6 → 13a ; 3 → 1

In this process, the formation of the aminoacetal intermediate (5) required the use of an expensive material, 3-thienaldehyde.

We wish now to report the synthesis of the intermediate hydroxy derivative (13a) starting from 2-thienaldehyde as well as a new process for the preparation of 2-substituted thieno[3,2-c]pyridines.

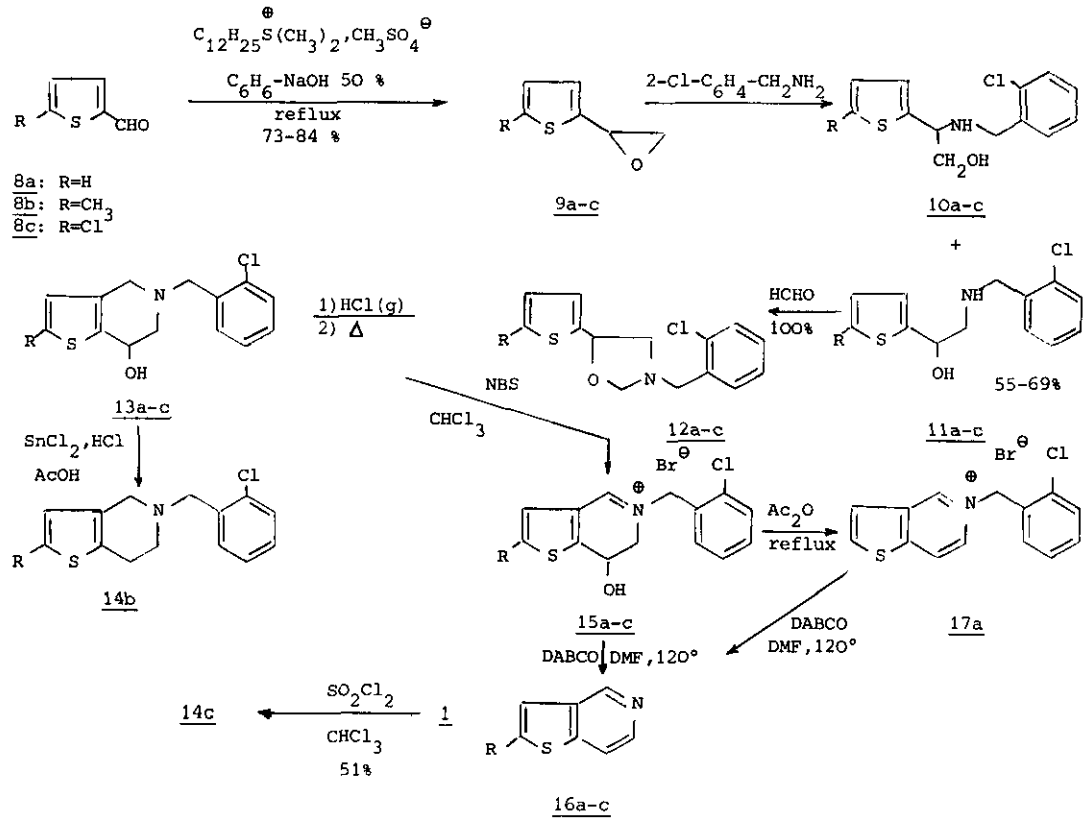
In 1962, Corey an Chaykovsky[6] realized the transformation of aldehydes and ketones into oxiranes by treatment with the sulfur ylid obtained by reacting trimethylsulfonium iodide with dimsylsodium in a tetrahydrofuran-dimethylsulfoxide solution.

It has been shown recently[7] that the same ylid could be generated in a biphasic system (50% sodium hydroxide solution-methylenechloride) in the presence of tetrabutylammonium iodide as phase transfer catalyst.

Such a process was convenient for the synthesis of styrene oxide (92%) but failed in our hands to produce 2-thienyloxirane from 2-thienaldehyde.

However, this reaction succeeded when carried out by using a long chain alkylated sulfonium salt without phase transfer catalyst according to Tagaki and coll.[8]. Accordingly, epoxides (9a-c) were easily obtained from thienaldehydes (8a-c) and dodecyldimethyl sulfonium methylsulfate[9] (scheme III).

SCHEME III



Among these compounds only (9a) had been previously prepared[10] from 2-chloro 1-(2-thienyl)ethanol. The oxirane ring opening with an excess of o-chlorobenzylamine at room temperature led to

a mixture of amino alcohols (10) and (11) from which (11) was isolated by fractionated crystallization. The treatment of oxiranes with other amines[9] allowed the preparation of amino alcohols analogs to (11), some of which had been previously described[11].

By condensation with formaldehyde in 40 % aqueous solution, (11a-c) gave the corresponding oxazolidines (12a-c); their hydrochlorides were thermically rearranged to thienopyridines (13a-c) by refluxing in toluene or diisopropylether ; this rearrangement was similar to that described by Kametani and coll.[12] for the preparation of isoquinolines.

Dehydroxylation of (13b) and (13c) with stannous chloride-hydrochloric acid in acetic acid gave the Ticlopidine analogs (14b) and (14c). The 2-chloro derivative (14c) was also obtained by direct chlorination of (1) with sulfuryl chloride according to the Godt and Wann process[13] used for the synthesis of other thiophen derivatives. Amino alcohols (13a-c) were also useful intermediates to the new corresponding thieno/3,2-c/pyridines (16a-c).

N-Bromosuccinimide oxidation of (13a-c) in chloroform at room temperature yielded (15a-c) which were immediately transformed into (16a-c) by heating at 120°C in dimethylformamide in the presence of 1,4-diazabicyclo/2.2.1./octane : indeed both reactions, the expected dequaternisation[14] and the dehydration, simultaneously occured. It was shown that the conversion of (15a) into (16a) could be carried out in two steps by dehydration with acetic anhydride followed by dequaternisation with DABCO in dimethylformamide.

N°	mp or bp/mmHg (°C)	Yield %	^{1}H. N.M.R. (ppm)
13a	199 - 201 (EtOH)	93	$CDCl_3$: 3,45(q,J=14;2) ; 3,75(s;2) ; 4,65(t;1) ; 6,85(q,J=5,5;2)
13b	189 - 191 (EtOH)	92	$CDCl_3$: 2,40(s;3) ; 3,45(q,J=14;2) ; 3,75(s;2) ; 4,60(t;1) ; 6,30(s;1)
13c	179 - 181 (EtOH)	82	$CDCl_3$: 3,40(q,J=14;2) ; 3,75(s;2) ; 4,55(t;1) ; 6,40(s;1)
14b	hydrochloride 188 - 190 (iPrOH)	63	$CDCl_3$: hydrochoride : 2,35(s;3) ; 4,15(s;2) ; 4,60(s;2) ; 6,35(s;1) ; 7,40(s;4)
14c	hydrochloride 208 - 210 (EtOH/H_2O)	60	$CDCl_3$: 2,75(s;4) ; 3,45(s;2) ; 3,75(s;2) ; 6,45(s;1)
15a	162-164 (EtOH)	56	(DMSO d_6) : 4,10(m;2) ; 5,40(t;1) ; 5,45(s;2) ; 7,75(q,J=5,5;2) ; 9,75(s;1)
15c	185 - 187 (EtOH)	89	(DMSO d_6) : 4,10(m;2) ; 5,30(t;1) ; 5,45(s;2) ; 9,55(s;1)
16a	47 - 49	60	litt. (15)
16b	hydrochloride 189 - 191 (EtOH)	58	$CDCl_3$: 2,45(s;3) ; 6,85(s;1) ; 7,55(d,J=5,5;1) ; 8,30(d,J=5,5;1) ; 8,85(s;1)
16c	85 - 86 /0,1 45 - 46	54	$CDCl_3$: 7,10(s;1) ; 7,50(d,J=5,5;1) ; 8,30(s,J=5,5;1) ; 8,80(S;1)
17a	201 - 203 (iPrOH)	64	(DMSO d_6) : 6,25(s;2) ; 8,25(q,J=5,5;2) ; 9,00(s;2) ; 10,05(s;1)

15b * was not isolated

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