

A NEW SYNTHESIS OF

4,5,6,7 - TETRAHYDROTHIENO[3,2-c]PYRIDINE

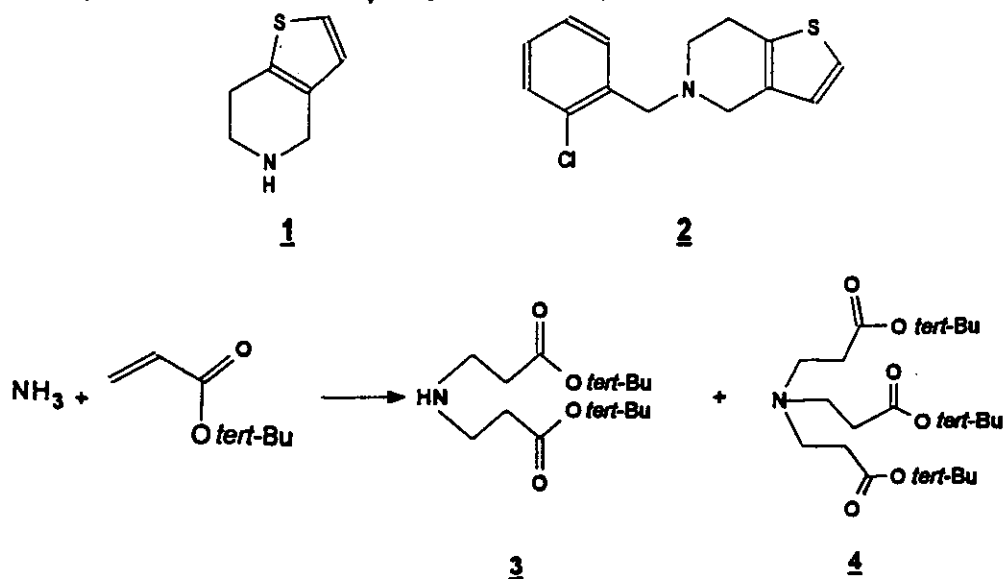
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Abstract - The title compound was prepared via a sequence containing as the key step a thiophene ring formation from a 1,4 - dicarbonyl intermediate.

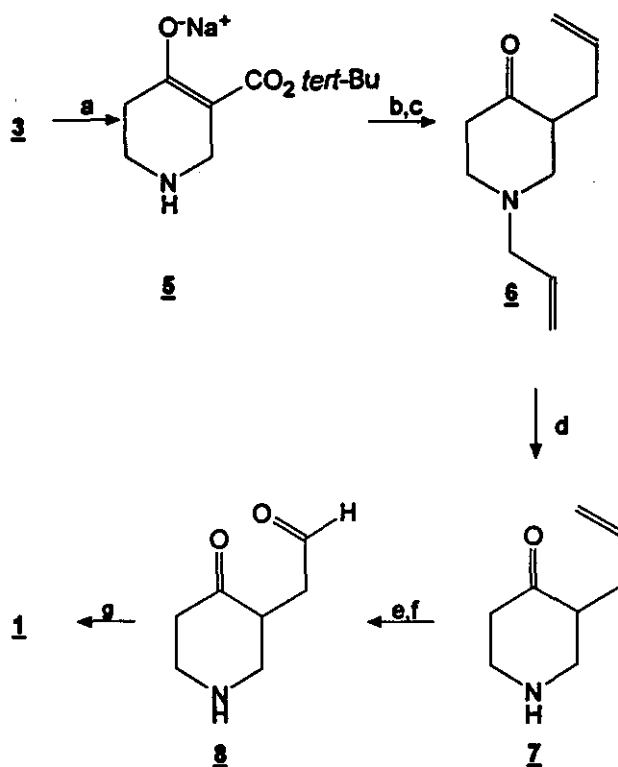
4,5,6,7-Tetrahydrothieno[3,2-c]pyridine (**1**) is a useful building block for the preparation of a platelet aggregation inhibitor Ticlopidine (**2**)¹ and related drugs.² The central problem in synthesising these drugs is the construction of the title ring system, which has previously been achieved starting from substituted thiophenes, by means of Pomeranz-Fritsch reaction,³ Friedel-Crafts acylation,⁴ cyclisation of thienylvinylisocyanates,⁵ Bischler-Napieralski reaction,⁶ Pictet-Spengler reaction,^{6,7} intramolecular azide-aldehyde condensation⁸ and electrocyclic pyridine ring closure.⁹ However, no practical syntheses of the parent ring system via formation of the thiophene ring have been reported.¹⁰ We now report the efficient synthesis of **1** based on a TiCl_4 -catalysed 1,4-dicarbonyl sulfurisation.¹¹



The starting material, di-*tert*-butyl 3,3-iminodipropionate (**3**), was prepared by the reaction of a 3.3 molar excess of ammonia to *tert*-butyl acrylate in an autoclave at 50°C for 4 days. The reaction afforded a 3:1 mixture of **3** and tertiary amine (**4**) (95% yield based on *tert*-butyl acrylate).

Isolation of **3** involved two consecutive amine hydrochloride salt precipitations with gaseous hydrochloric acid from ether, which gave, after treatment with aqueous sodium hydroxide and extraction, the pure free base (**3**) ¹² in 56% yield based on *tert*-butyl acrylate. As shown in Scheme I, the Dieckmann condensation of the amine (**3**) performed with 1.2 equivalents of sodium hydride gave the sodium enolate (**5**) (which did not need to be isolated) in 65% yield. Treatment of **5** with a further 1.2 equivalents of sodium hydride and 2.5 equivalents of allyl bromide gave, after acid hydrolysis of the *tert*-butyl ester and decarboxylation, the *C,N*-diallylated piperidone (**6**) ¹³ in a disappointing 32% yield.

Scheme I



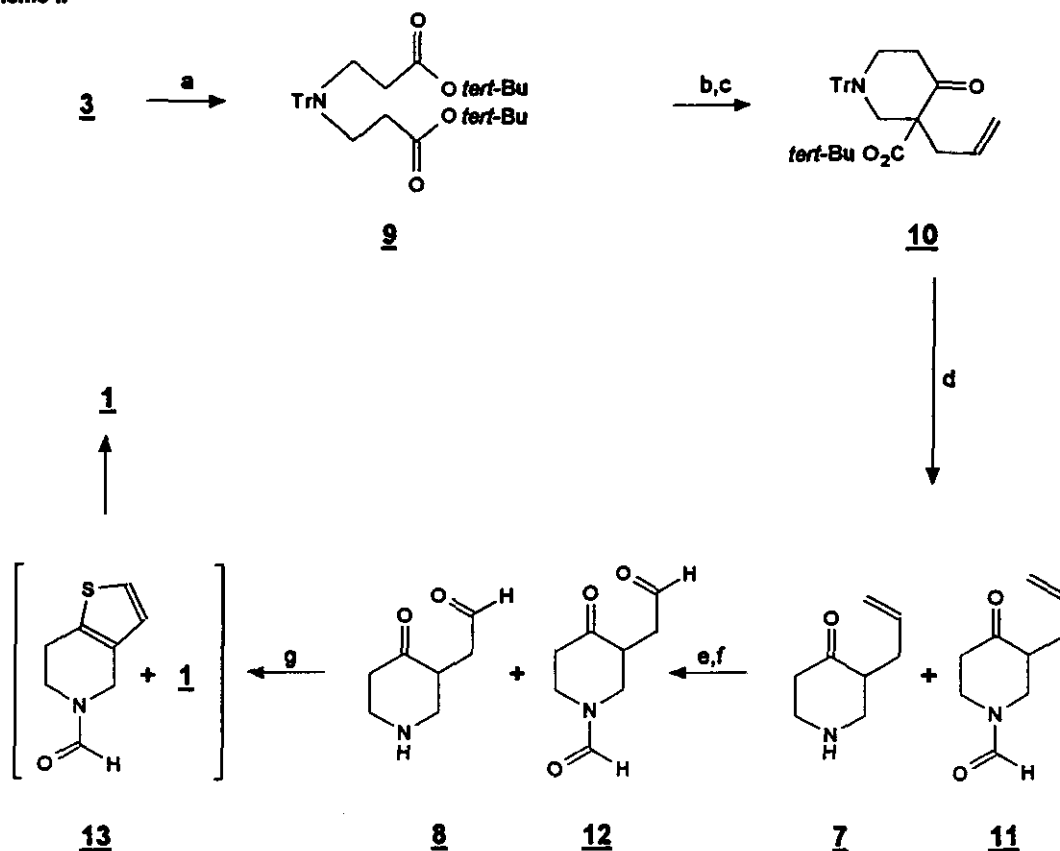
Reagents and conditions:

a) NaH(1.2 eq.), DMF, 75°C (65%); b) NaH(1.2 eq.), $\text{CH}_2=\text{CH}-\text{CH}_2-\text{Br}$ (2.5 eq.), DMF, 25°C; c) 0.5N HCl, reflux, 1.5 h (32% from **5**); d) 8 mol% $\text{RhCl}(\text{PPh}_3)_3$, MeCN / H_2O 5:1, reflux, 5 h (56%); e) CF_3COOH (2.3 eq.), O_3 , CH_2Cl_2 / MeOH 6:1, -60°C; f) Me_2S (1.4 eq.), 0°C; g) $\text{HCl}_{(g)}$, $\text{H}_2\text{S}_{(g)}$, TiCl_4 (4 eq.), 0°C to 20°C, 24 h (94% from **7**).

The Rh-catalysed hydrolytic *N*-deprotection ¹⁴ gave a 56% yield of piperidone (**7**).¹⁵ This was ozonolysed in the presence of trifluoroacetic acid to protect the amino group against oxidation, to give the labile 1,4-dicarbonyl compound (**8**). The reaction mixture was treated, without isolation of **8**, with gaseous H₂S and HCl in presence of TiCl₄¹¹ to afford the requisite bicycle (**1**)¹⁶ in 94% yield.

The low yield of the crucial steps of the above synthesis compelled us to look for another protecting group for the ring nitrogen.

Scheme II



Reagents and conditions:

- a) TrCl(1.0 eq.), Et₃N(1.1 eq.), CH₂Cl₂, 25°C, 18 h (95%); b) *tert*-BuOK(1.2 eq.), toluene, 75°C, 45 min;
 c) $\text{CH}_2=\text{CH}-\text{CH}_2-\text{Br}$ (1.2 eq.), *tert*-BuOH, 40°C, 1 h (84% from **9**); d) HCOOH, reflux, 2 h (1:1 mixture of **7** and **11**, 79%);
 e) CF₃COOH(2.3 eq.), O₃, CH₂Cl₂ / MeOH 6:1, -60°C; f) Me₂S(1.4 eq.), 0°C; g) HCl(g), H₂S(g), TiCl₄(4 eq.), CH₂Cl₂ / MeOH 2:1, 0°C to 50°C, 48 h (88% from **7** + **11** mixture).

Thus, secondary amine (3) was protected with the trityl group ¹⁷ and the resulting tertiary amine (9) ¹⁸ was submitted to an analogous sequence of steps as in the first version (Scheme II).

Cyclisation of 9 followed by allylation of the resulting enolate gave the intermediate (10) ¹⁹ in 84% yield. Refluxing 10 in formic acid for 2 h resulted in the cleavage of both the tritylamine and the *tert*-butyl ester followed by decarboxylation. Partial formylation of nitrogen was inevitable and the reaction mixture contained 7, 11 and trityl formate in a 1:1:2 ratio. The solubility of the latter compound in hexane and solubility of 11 ²⁰ in water allowed the extractive separation of all three compounds. However, the mixture of 7 and 11 (79% total yield based on 10) could be ozonolysed without further separation and furnished the mixture of 8 and *N*-formylated derivative (12). This mixture was submitted to the thiophene ring closure reaction, which gave the mixture of 1 and *N*-formylated (13) ²¹ under mild conditions (20°C, 24 h). However, somewhat harsher reaction conditions (50°C, 48 h) led to the simultaneous cleavage of the *N*-formyl group, thus affording 1 in 68% yield from the 7 + 11 mixture, after bulb-to-bulb distillation.

Similar methodology was applied by us to the synthesis of Ticlopidine.²²

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12. 3: Nmr (CDCl₃, 300 MHz) δ : 3.85 (t, J=7 Hz, 4H); 2.43 (t, J=7 Hz, 4H); 1.61 (b s, 1H); 1.47(s, 18H).
13. 6: Nmr (300 MHz, CDCl₃) δ : 5.97 - 5.83 (m, 1H); 5.81 - 5.69 (m, 1H); 5.20 (d, J=18 Hz, 1H); 5.18 (d, J=10 Hz, 1H); 5.05 (d, J=18 Hz, 1H); 5.03 (d, J=8 Hz, 1H); 3.18 - 3.03 (m, 4H); 2.66 - 2.51 (m, 3H); 2.47 - 2.33 (m, 2H); 2.15 (t, J=10 Hz, 1H); 2.03 (q, J=8 Hz, 1H).
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15. 7: Nmr (300 MHz, CDCl₃) δ : 5.85 - 5.71 (m, 1H); 5.07 (d, J=17 Hz, 1H); 5.01 (d, J=10 Hz, 1H); 3.45 - 3.33 (m, 2H); 3.01 - 2.91 (m, 1H); 2.65 - 2.38 (m, 1H); 2.06 - 1.96 (m, 1H); 1.75 (b s, 1H).
16. 1: Nmr (300 MHz, CDCl₃) δ : 7.07 (d, J=5 Hz, 1H); 6.74 (d, J=5 Hz, 1H); 3.93 (s, 2H); 3.15 (t, J=5.5 Hz, 2H); 2.81 (t, J=5.5 Hz, 2H); 1.78 (b s, 1H).
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18. 9: Nmr (300 MHz, CDCl₃) δ : 7.48 (d, J=8.5 Hz, 6H); 7.30 - 7.23 (m, 6H); 7.15 (t, J=7 Hz, 3H); 2.75 (t, J=7.5 Hz, 4H); 2.36 (t, J=7.5 Hz, 4H); 1.41 (s, 18H).
19. 10: Nmr (300 MHz, CDCl₃) δ : 7.60 - 7.38 (b s, 6H); 7.38 - 7.22 (m, 6H); 7.22 - 7.10 (m, 6H); 5.86 - 5.71 (m, 1H); 5.00 (d, J=15 Hz, 1H); 4.95 (d, J=10 Hz, 1H); 3.63 (d, J=10 Hz, 1H); 3.23 - 3.08 (m, 2H); 2.44 - 2.20 (m, 3H); 1.83 (d, J=10 Hz, 1H); 1.62 (s, 10H).
20. 11: Nmr (300 MHz, CDCl₃) 2 isomeric amides 1:1, δ : 8.22 and 8.17 (2s, 1H); 5.85 - 5.68 (m, 1H); 5.13 (d, J=10 Hz, 1H); 5.10 (d, J=5 Hz, 1H); 4.49 - 4.40 and 4.38 - 4.26 (2m, 1H); 3.93 - 3.84 (m, 1H); 2.57 - 3.47 and 3.40 - 3.30 (2m, 1H); 3.21 and 2.94 (2dd, J=13 Hz, 9.5 Hz, 1H); 2.64 - 2.46 (m, 4H); 2.18 - 2.04 (m, 1H).
21. 13: Nmr (300MHz, CDCl₃) 2 isomeric amides 3:2, δ : 8.26 and 8.20 (2s, 2:3, 1H); 7.17 (d, J=5 Hz, 1H); 6.81 and 6.80 (2d, 3:2, J=5 Hz, 1H); 4.62 and 4.49 (2s, 3:2, 2H); 3.88 and 3.71 (2t, 2:3, J=5.5 Hz, 2H); 2.97 - 2.88 (m, 2H).
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