A NEW SYNTHESIS OF 4,5,6,7 - TETRAHYDROTHIENO[3,2-*c*]PYRIDINE

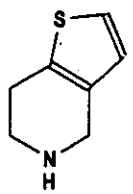
Aleksander Warm

LONZA AG, Research & Development

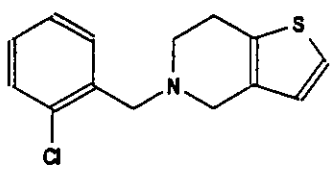
CH-3930 Visp, Switzerland

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

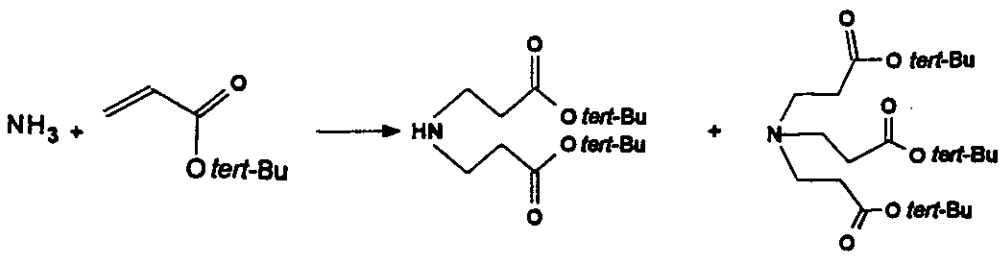
4,5,6,7-Tetrahydrothieno[3,2-*c*]pyridine (1) is a useful building block for the preparation of a platetet aggregation inhibitor Ticlopidine (2)[1] and related drugs.[2] The central problem in synthesising these drugs is the construction of the title ring system, which has previously been achieved starting 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 condensation[8] 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]



1



2

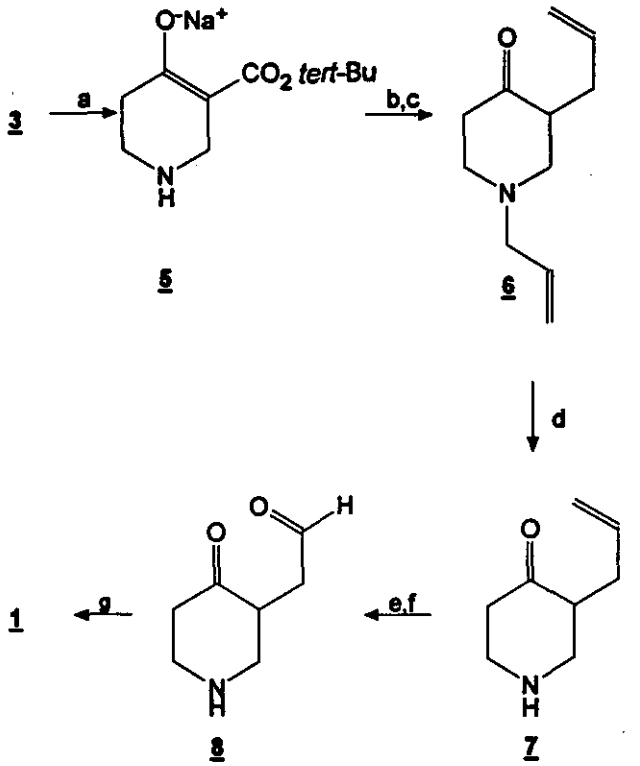


3 4

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



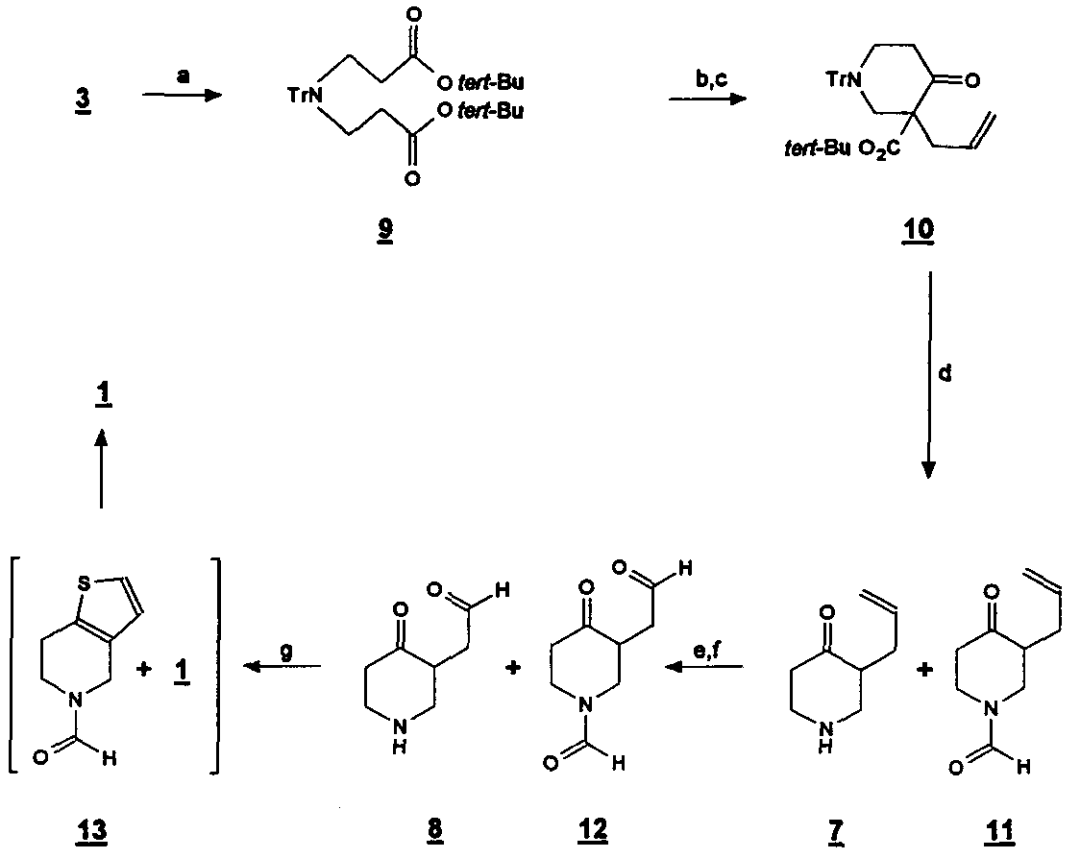
Reagents and conditions:

a) NaH(1.2 eq.), DMF, 75°C (65%); b) NaH(1.2 eq.),  Br (2.5 eq.), DMF, 25°C; c)0.5N HCl, reflux, 1.5 h (32% from 5); d) 8 mol% $RhCl(PPh_3)_3$, 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) $HCl_{(g)}$, $H_2S_{(g)}$, $TiCl_4$(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 H_2S and HCl in presence of $TiCl_4$[11] 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.), Et_3N(1.1 eq.), CH_2Cl_2, 25°C, 18 h (95%); b) *tert*-BuOK(1.2 eq.), toluene, 75°C, 45 min;

c)  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) CF_3COOH(2.3 eq.), O_3, CH_2Cl_2 / MeOH 6:1, -60°C; f) Me_2S(1.4 eq.), 0°C; g) $HCl_{(g)}$, $H_2S_{(g)}$, $TiCl_4$(4 eq.), CH_2Cl_2 / MeOH 2:1, 0°C to 50°C, 48 h (68% 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]

REFERENCES AND NOTES

1. E. Saltiel and A. Ward, *Drugs*, 1987, **34**, 222 - 262.
2. D. Aubert, C. Ferrand and J-P. Maffrand, *EP 99 802* (Sanofi) (*Chem. Abstr.*,1984, **100**, 191856z).
3. W. Herz and L. Tsai, *J. Am. Chem. Soc.*, 1953, **75**, 5122; *DE 2530516* (Parcor) (*Chem. Abstr.*,1976, **84**, 135620g); J-P. Maffrand and J. Eloy, *J. Heterocycl. Chem.*, 1976, **13**, 1347.
4. K. Satake, T. Imai, M. Kimura and S. Morosawa, *Heterocycles*, 1981, **16**, 1271.
5. F. Eloy and A. Deryckere, *Bull. Soc. Chim. Belg.*, 1970, **79**, 301.
6. S. Gronowitz and E. Sandberg, *Ark. Kemi*, 1970, **32**, 217.
7. E. Braye, *US 4127580* (Parcor) (*Chem. Abstr.*,1979, **90**, 87431w); J-P. Maffrand and R. Boigegrain, *Heterocycles*, 1979, **12**, 1479.
8. M. Farnier, S. Soth and P. Fournari, *Can. J. Chem.*, 1976, **54**, 1066.
9. S. Hibino, S. Kano, N. Mochizuki and E. Sugino, *J. Org. Chem.*, 1984, **49**, 5006.
10. L.H. Klemm and D.R. McCoy, *J. Heterocycl. Chem.*, 1969, **6**, 73.
11. E. Campaigne and W.O. Foye, *J. Org. Chem.*, 1952, **17**, 1405; for a review see *Comprehensive Heterocyclic Chemistry*, ed. by A.R. Katritzky, **4**, Pergamon Press, Oxford, 1984, pp. 884 - 888.

12. **3:** Nmr ($CDCl_3$, 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, $CDCl_3$) 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).

14. B.C. Laguzza and B. Ganem, *Tetrahedron Lett.*, 1981, **22**, 1483.

15. **7:** Nmr (300 MHz, $CDCl_3$) 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. $CDCl_3$) 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).

17. A. Badorc, D. Frehel, J-P. Maffrand and E. Vallee, *EP 0192535* (Sanofi), (*Chem. Abstr.*,1987, **107**, 89900s).

18. **9:** Nmr (300 MHz, $CDCl_3$) 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, $CDCl_3$) 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, $CDCl_3$) 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, $CDCl_3$) 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).

22. J. Gosteli and A. Warm, *EP 360293* (Lonza) (*Chem. Abstr.*,1990, **113**, 97595k).

Received, 13th July, 1992