View Article Online / Journal Homepage / Table of Contents for this issue

A Versatile and Stereocontrolled Synthesis of Quinolizidines and Indolizidines using Trialkylsilyl Trifluoromethanesulphonate: Total Synthesis of (\pm) -Tylophorine

Masataka Ihara,^a Mayumi Tsuruta,^a Keiichiro Fukumoto,*^a and Tetsuji Kametani^b

^a Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

^b Institute of Medicinal Chemistry, Hoshi University, Ebara 2–4–41, Shinagawa-ku, Tokyo 142, Japan

Quinolizidines and indolizidines were synthesised by reaction of α , β -unsaturated enamide esters with trialkylsilyl trifluoromethanesulphonate and triethylamine in dichloromethane; a short total synthesis of (±)-tylophorine (**16**) was achieved *via* annelation.

Recently we reported a new synthetic route to quinolizidine and indolizidine derivatives by the intramolecular Diels– Alder reaction of 1-aza-1,3-dienes (2).^{1,2} The reaction was performed by heating the mixture of enamide ester (1), trimethylsilyl chloride, Et₃N, and ZnCl₂ in toluene or *o*-dichlorobenzene at 180 °C (Scheme 1). Altering the reaction conditions for the annelation led us to find a very effective and mild set of conditions. We now report a novel cyclisation reaction catalysed by trialkylsilyl trifluoromethanesulphonate and an application to the synthesis of tylophorine (16).[†]

[†] All new compounds gave analytical and spectral data in agreement with the proposed structures.





The annelation was accomplished by reaction of the enamide esters with an equimolar amount of trialkylsilyl trifluoromethanesulphonate and Et_3N in CH_2Cl_2 at ambient temperature (Scheme 2). Thus treatment of (4)¹ with t-butyldimethylsilyl trifluoromethanesulphonate (TBSOTf) or trimethylsilyl trifluoromethanesulphonate (TMSOTf) in the presence of Et_3N in CH_2Cl_2 for 1 h at 15 °C followed by the usual work-up, gave the benzo[a]quinolizidine (5)¹ in 83 or 75% yields. The reaction of (6)² with TBSOTf under the same conditions afforded two indolizidines (7)² and (8),² in 78 and 5% yields, respectively. The reaction did not proceed in the absence of Et_3N , and treatment of the enamide esters with other Lewis acids, such as $BF_3 \cdot Et_2O$, TiCl₄, and Et_2AlCl , yielded none of the desired products.

A short synthesis of (\pm) -tylophorine (16),³ an antineoplastic alkaloid, was achieved according to the above methodology (Scheme 3). The acid $(9)^4$ was converted into the acid chloride and then condensed with 4-aminobutyraldehyde diethyl acetal to give the amide (10) in quantitative yield. Deprotection of



Scheme 3. Reagents: i, $(COCl)_2$; ii, $H_2N[CH_2]_3CH(OEt)_2$, $NaHCO_3$; iii, AcOH, H_2O ; iv, $Ph_3P=CHCO_2Et$; v, TBSOTf, Et_3N , room temp.; vi, TTFA, BF₃ · Et₂O, TFA; vii, KOH, MeOH; viii, HMPA, 230 °C; ix, NaAl(OCH₂CH₂OMe)₂H₂.

the acetal (10) using dilute AcOH, followed by Wittig reaction formed, in 93% yield, the enamide ester (11), which was subjected to the annelation using TBSOTf and Et₃N in CH_2Cl_2 for 5.5 h at 15 °C. The stereo-structure (12) of the product, m.p. 165-167 °C, isolated in 68% yield after purification by chromatography on silica gel, was deduced on the basis of the spectral analysis, $[\delta_{\rm H} ({\rm CDCl}_3) 0.95 (3{\rm H}, {\rm t}, J 8$ Hz, OCH₂CH₃), 3.72, 3.75, and 3.80 (3H, 3H, and 6H, each s, $4 \times \text{OMe}$, 3.88 (2H, q, J 8 Hz, OCH₂CH₃)]. Oxidation of (12) with two moles of thallium(III) trifluoroacetate (TTFA) and BF₃ · Et₂O in a mixture of CH₂Cl₂ and CF₃CO₂H (TFA)⁵ for 16 h at 4 °C produced in 83% yield the pentacyclic compound (13), m.p. 267–271 °C [$\delta_{\rm H}$ (CDCl₃) 1.46 (3H, t, J 8 Hz, OCH_2CH_3), 3.93 and 4.10 (3H and 9H, each s, 4 × OMe), 7.20, 7.73, 7.75, and 8.79 (each 1H, each s, $4 \times \text{ArH}$) Hydrolysis of (13), followed by decarboxylation of the resulting acid (14) $[\delta_{\rm H} (\rm CDCl_3) 8.80 (1H, s, ArH)]$, conducted by heating a solution in hexamethylphosphoric triamide (HMPA) at 230 °C for 3 h, furnished (\pm) -9-oxotylophorine (15), m.p. 282–283 °C (lit.,^{3b} m.p. 280–281 °C) in 65% overall yield. Reduction of (15) with sodium bis(2methoxyethoxy)aluminium hydride in refluxing dioxane for 2 h gave (\pm) -tylophorine (16) in 87% yield. \ddagger

 $[\]ddagger$ It was reported that reduction of (±)-9-oxotylophorine with LiAlH₄ or B₂H₆ gave poor results, ref. 3b.

We thank Professors H. Iida and C. Kibayashi of Tokyo College of Pharmacy, for their kind gift of spectral data of (\pm) -9-oxotylophorine and (\pm) -tylophorine.

Received, 19th April 1985; Com. 522

References

- 1 M. Ihara, T. Kirihara, A. Kawaguchi, K. Fukumoto, and T. Kametani, *Tetrahedron Lett.*, 1984, **25**, 4541.
- 2 M. Ihara, T. Kirihara, K. Fukumoto, and T. Kametani, *Hetero-cycles*, 1985, 23, 1097.
- 3 Recent synthesis (a) J. E. Cragg, R. B. Herbert, F. B. Jackson, C. J. Moody, and I. T. Nicholson, J. Chem. Soc., Perkin Trans. 1, 1982, 2477; (b) H. Iida, Y. Watanabe, M. Tanaka, and C. Kibayashi, J. Org. Chem., 1984, 49, 2412 and references cited therein.
- 4 J. H. Russel and H. Hunziker, Tetrahedron Lett., 1969, 4035.
- 5 E. C. Taylor, J. G. Andrade, G. J. H. Rall, and A. McKillop, J. Am. Chem. Soc., 1980, 102, 6513.