Trifluoromethanesulfonic Anhydride–4-(*N*,*N*-Dimethylamino)pyridine as a Reagent Combination for Effecting Bischler–Napieralski Cyclisation under Mild Conditions: Application to Total Syntheses of the *Amaryllidaceae* Alkaloids *N*-Methylcrinasiadine, Anhydrolycorinone, Hippadine and Oxoassoanine

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A combination of triflic anhydride and 4-(N,N-dimethylamino)pyridine effects Bischler–Napieralski cyclisation of β -phenethylcarbamates and β -phenethylamides under very mild conditions.

The Bischler-Napieralski cyclisation of β-phenethylamides has provided a powerful method for construction of 3,4-dihydroisoquinolines and related heterocyclic molecules.1 Almost invariably, however, such conversions require the use of both high temperatures and aggressive reagents such as phosphorus oxychloride (POCl₃). Consequently, substrates containing sensitive functionality often do not survive these conditions. This situation has prompted efforts² to identify alternative reagents which would allow efficient cyclisation to be achieved under milder conditions, but only modest success has been achieved in this regard. In connection with studies³ directed towards the synthesis of various Amaryllidaceae alkaloids,4 we have discovered that a combination of trifluoromethanesulfonic (triflic) anhydride (Tf₂O) and 4-(*N*,*N*- dimethylamino)pyridine (DMAP) can effect cyclo-condensation of both β -phenethylcarbamates and β -phenethylamides at or below room temperature. In a number of instances successful cyclisation is achieved under such conditions while POCl₃ fails to effect any reaction whatsoever even at temperatures as high as 200 °C. Given its potentially broad synthetic utility, we now report on the title reagent combination and its capacity to effect Bischler-Napieralski cyclisation of a range of substrates.

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The efficacy of the title reagent combination is highlighted by the results shown in entry 1 of Table 1. Thus, carbamate 1^{3b} does not react with POCl₃ even at 200 °C but treatment of this compound with Tf₂O–DMAP (5:3 molar ratio w.r.t. 1) at 0–

15

16

RO

B(OH)₂

ÒR

17

a R-R = -CH2-

b R = Me

15 °C for 10 h gave, after aqueous work-up, the alkaloid *N*methylcrinasiadine $2^{3b,5}$ in 92% yield. The success of such reactions was critically dependent upon the molar ratios of Tf₂O and DMAP employed. The most favourable conditions uncovered so far require *ca*. 5 molar equivalents (w.r.t. substrate) of Tf₂O and *ca*. 3 molar equivalents of DMAP. Employing an excess of Tf₂O w.r.t. DMAP appears to be essential since using the two reagents in equimolar amounts is ineffective. Furthermore, Tf₂O alone fails to achieve clean cyclisation.

The capacity of Tf₂O–DMAP to achieve clean cyclisation of systems possessing sensitive functionality is exemplified by the results shown in entries 2–4. Thus, compounds 3^{3d} and 5^{3d} undergo conversion into 2-deoxylycoricidine diacetate 4^{3d} and the pancratistatin analogue $6,^{3d}$ respectively, on treatment with Tf₂O–DMAP.[†] Attempts to effect the same conversions with POCl₃ only resulted in extensive decomposition of the substrates. Reaction of carbamate 7^{3a} with Tf₂O–DMAP (at 0 °C for 2 h) gave the lactam **8** (85%) (mp 148–151 °C; lit.⁶ mp 144–147 °C) while POCl₃-promoted cyclisation required temperatures of 80 °C and reaction times of 16 h to ensure complete consumption of the substrate **7** and under such conditions a mixture of compound **8** (46%) and double-bond isomer **15** (46%) (mp 170–172 °C; lit.⁷ mp 166–168 °C) was obtained.

The discovery of new and mild conditions for effecting Bischler–Napieralski cyclisation has allowed the development of abbreviated syntheses of the pyrrolophenanthridinone alkaloids anhydrolycorinone $10^{6.8}$ and oxoassoanine $12^{.5a,8b,8f,9}$ These natural products have been the subject of a number of synthetic studies^{5a,6,8,9} largely because of their interesting biological activities.⁴ The substrate 9, required for the anticipated cyclisation reaction leading to anhydrolycorinone, was prepared by the three-step sequence shown in Scheme 1. Thus, readily available 7-bromoindole 16^{10} was subjected to Suzuki cross-coupling¹¹ with arylboronic acid $17a.^{3,12}$ The double bond in the resulting biaryl $18a^{\ddagger}$ (99%) (mp 119–121 °C) was then removed by ionic hydrogenation¹³ and the corresponding dihydro-compound 19a (83%) thereby obtained. Finally, dihydroindole 19a was converted into the carbamate 9 (90%) (mp

> . CO₂Me



ÓΒ

− 18 x,y = double bond
► 19 x,y = single bond

BO

iii

RO

ÔR

11 R = Me

9 R-R = -CH₂-

102–104 °C) by reaction with methyl chloroformate and sodium *hydride*. While POCl₃ failed to effect cyclisation, treatment of substrate **9** with $Tf_2O-DMAP$ (entry 5, Table 1) gave

anhydrolycorinone **10**^{6,8} in 88% yield.§ 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) promoted dehydrogenation⁸^c of compound **10** resulted in the efficient (71%) formation of the

Table 1 Tf₂O–DMAP-promoted Bischler–Napieralski cyclisation reactions.





alkaloid hippadine **20**^{8b-f,14} (mp 216–218 °C; lit.^{14c} mp 215–217 °C).

The synthesis of oxoassoanine 12 followed along similar lines to those used in the preparation of congener 10. Thus, boronic acid 17b¹⁵ was coupled with indole 16 and the resulting biaryl 18b (93%) (mp 273–274 °C) then subjected to ionic hydrogenation. The dihydro-compound 19b (77%) (mp 93–94 °C) formed in this manner was converted into the corresponding carbamate 11 (96%) (mp 101–102 °C), cyclisation of which (entry 6, Table 1) gave natural product 12 (76%) (mp 277–278 °C; lit.^{9b} mp 276–277 °C) together with regioisomer 21 (7%) (mp 162–164 °C).

The Tf₂O–DMAP reagent system also provides an effective means for converting β -phenethylamides into the corresponding 3,4-dihydroisoquinoline (entry 7, Table 1). Thus, the bisamide **13**¹⁶ is readily converted into the tetracycle **14** (78%) (mp 199–201 °C; lit.¹⁶ mp 198–202 °C) on treatment with Tf₂O–DMAP and the structure of the product has been confirmed by X-ray analysis.¶ While the same conversion can be effected with POCl₃ a lower yield (60%) of an impure product is obtained.¹⁶

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Footnotes

† In these reactions the primary cyclisation products are imidates which are subjected to acid-catalysed hydrolysis in order to generate the desired lactams. However, such conditions also result in partial acetate hydrolysis and, so, a reacetylation step is required.

- ‡ All new compounds had spectroscopic data (IR, UV–VIS, NMR, MS) consistent with the assigned structure. Satisfactory combustion and/or HRMS analytical data were obtained for new compounds and/or suitable derivatives.
- § Representative procedure for Bischler–Napieralski cyclisation: A 1.10 mol dm⁻³ solution of Tf₂O (1.05 ml, 1.16 mmol) in anhydrous CH₂Cl₂ was added over a period of 15 min to a cooled (ice–water bath) solution of carbamate 9 (69 mg, 0.23 mmol) and DMAP (85 mg, 0.69 mmol) in CH₂Cl₂ (6 ml). The reaction mixture was left to stir for 16 h while the ice-bath was kept in place but no further additions of ice were made. The reaction mixture was then diluted with CH₂Cl₂ (10 ml), washed with saturated aqueous Na₂CO₃ (1 × 5 ml), 20 % v/v aqueous acetic acid (1 × 5 ml) and then saturated aqueous Na₂CO₃ (1 × 5 ml) before being dried over Na₂SO₄. The reaction mixture was filtered and the filtrate concentrated under reduced pressure to give a light brown solid which was recrystallised (twice from

MeOH) to give anhydrolycorinone (40 mg) as fine white needles, mp 236–238 °C (lit.^{8/} mp 245 °C). The mother liquors were subjected to preparative thick layer chromatography (silica, 2:8 acetone–benzene elution). The single major and chromophoric band (R_f 0.5) was extracted (CHCl₃) to give additional anhydrolycorinone (13 mg, 88% combined yield). If isoquinolines are being formed in the cyclisation reaction then the acetic acid wash and the second Na₂CO₃ wash described in the above workup are omitted. The required isoquinoline and 4-(N_r N-dimethylamino)pyridine are then separated from one another by chromatography on alumina.

 \P Details have been been deposited with the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

References

- 1 G. Fodor and S. Nagubandi, Tetrahedron, 1980, 36, 1279.
- 2 S. Nagubandi and G. Fodor, *Heterocycles*, 1981, **15**, 165. For related efforts concerning the Ritter and Vilsmeier-Haack reactions see: A. García-Martinez, R. Martínez Alvarez, E. Teso Vilar, A. García Fraile, M. Hanack and L. R. Subramanian, *Tetrahedron Lett.*, 1989, **30**, 581; A. García-Martínez, R. Martínez Alvarez, J. Osío Barcina, S. de la Moya Cerero, E. Teso Vilar, A. García Fraile, M. Hanack and L. R. Subramanian, *J. Chem. Soc., Chem. Commun*, 1990, 1571.
- 3 (a) M. G. Banwell and A. Wu, J. Chem. Soc., Perkin Trans. 1, 1994, 2671; (b) M. G. Banwell and C. J. Cowden, Aust. J. Chem., 1994, 47, 2235; (c) M. G. Banwell, C. J. Cowden and I. C. S. Ho, J. Nat. Prod., 1994, 57, 1746; (d) M. G. Banwell, C. J. Cowden and R. W. Gable, J. Chem. Soc., Perkin Trans. 1, 1994, 3515.
- 4 For a comprehensive review concerning the isolation, structure elucidation, biological properties and synthetic approaches to the *Amaryllidaceae* alkaloids see: S. F. Martin, in *The Alkaloids*, ed. A. Brossi, Academic Press, New York, 1987, vol. 30, pp. 251–376. See also J. R. Lewis, *Nat. Prod. Rep.*, 1995, **12**, 339 and references cited therein.
- 5 For previous syntheses of *N*-methylcrinasiadine see: A. Mondon and K. Krohn, *Chem. Ber.*, 1972, **105**, 3726; R. K. Y. Zee-Cheng, S.-J. Yan and C. C. Cheng, *J. Med. Chem.*, 1978, **21**, 199; J. Grimshaw, R. Hamilton and J. Trocha-Grimshaw, *J. Chem. Soc.*, *Perkin Trans. 1*, 1982, 229; W. R. Bowman, H. Heaney and B. M. Jordan, *Tetrahedron*, 1991, **47**, 10119.
- 6 D. B. Grotjahn and K. P. C. Vollhardt, Synthesis, 1993, 579.
- 7 H. Iida, S. Aoyagi and C. Kibayashi, J. Chem. Soc., Perkin Trans 1, 1975, 2502.
- 8 For previous syntheses of anhydrolycorinone see: (a) H. Hara, O. Hoshino and B. Umezawa, *Tetrahedron Lett.*, 1972, 5031; (b) D. St. C. Black, P. A. Keller and N. Kumar, *Tetrahedron Lett.*, 1989, **30**, 5807; (c) M. A. Siddiqui and V. Snieckus, *Tetrahedron Lett.*, 1990, **31**, 1523; (d) U. Lauk, D. Duerst and W. Fischer, *Tetrahedron Lett.*, 1991, **32**, 65; (e) R. Grigg, A. Teasdale and V. Sridharan, *Tetrahedron Lett.*, 1991, **32**, 3859; (f) M. Iwao, H. Takehara, S. Obata and M. Watanabe, *Heterocycles*, 1994, **38**, 1717.
- 9 For previous syntheses of oxoassoanine see: (a) A. I. Meyers and R. H. Hutchins, *Tetrahedron Lett.*, 1993 34, 6185; (b) J. S. Parnes, D. S. Carter, L. J. Kurz and L. A. Flippin, J. Org. Chem., 1994, 59, 3497.
- 0 G. Bartoli, G. Palmieri, M. Bosco and R. Dalpozzo, *Tetrahedron Lett.*, 1989, 30, 16.
- 11 G. M. Carrera and G. S. Sheppard, Synlett., 1994, 93.
- 12 E. M. Campi, W. R. Jackson, S. M. Marcuccio and C. G. M. Naeslund, J. Chem. Soc., Chem. Commun., 1994, 2395.
- 13 G. Gribble and J. Hoffmann, Synthesis, 1977, 859.
- 14 For previous syntheses of hippadine see: (a) S. Prabhakar, A. N. Lobo and M. M. Marques, J. Chem. Res., 1987, (S) 167; (b) K. Hayakawa, T. Yasukouchi and K. Kanematsu, Tetrahedron Lett., 1987, 28, 5895; (c) T. Sakamoto, A. Yasuhara, Y. Kondo and H. Yamanaka, Heterocycles, 1993, 36, 2597.
- 15 R. B. Miller and J. J. Svoboda, Synth. Commun., 1994, 24, 1187.
- 16 M.-A. Siegfried, H. Hilpert, M. Rey and A. S. Dreiding, *Helv. Chim. Acta*, 1980, **63**, 938.