

## 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

Martin G. Banwell<sup>\*a</sup> Brett D. Bissett,<sup>a,b</sup> Stefan Busato,<sup>c</sup> Cameron J. Cowden,<sup>b</sup> David C. R. Hockless,<sup>a</sup> Jeffrey W. Holman,<sup>a</sup> Roger W. Read<sup>c</sup> and Angela W. Wu<sup>b</sup>

<sup>a</sup> Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200, Australia

<sup>b</sup> School of Chemistry, The University of Melbourne, Parkville, Victoria 3052, Australia

<sup>c</sup> School of Chemistry, The University of New South Wales, Sydney, NSW 2052, Australia

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

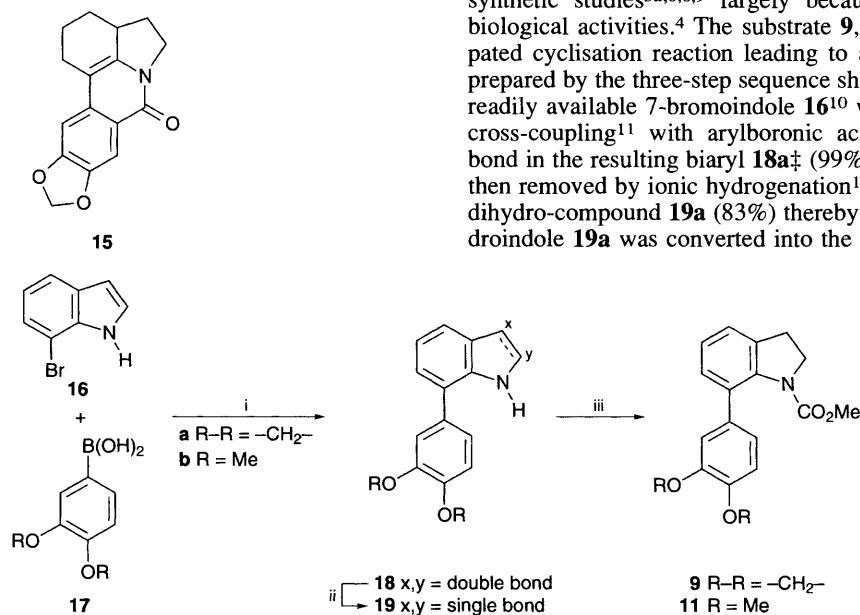
The Bischler–Napieralski cyclisation of  $\beta$ -phenethylamides has provided a powerful method for construction of 3,4-dihydroisoquinolines and related heterocyclic molecules.<sup>1</sup> Almost invariably, however, such conversions require the use of both high temperatures and aggressive reagents such as phosphorus oxychloride (POCl<sub>3</sub>). Consequently, substrates containing sensitive functionality often do not survive these conditions. This situation has prompted efforts<sup>2</sup> 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 studies<sup>3</sup> directed towards the synthesis of various *Amaryllidaceae* alkaloids,<sup>4</sup> we have discovered that a combination of trifluoromethanesulfonic (triflic) anhydride (Tf<sub>2</sub>O) and 4-(*N,N*-dimethylamino)pyridine (DMAP) can effect cyclo-condensation of both  $\beta$ -phenethylcarbamates and  $\beta$ -phenethylamides at or below room temperature. In a number of instances successful cyclisation is achieved under such conditions while POCl<sub>3</sub> 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.

The efficacy of the title reagent combination is highlighted by the results shown in entry 1 of Table 1. Thus, carbamate **13<sup>b</sup>** does not react with POCl<sub>3</sub> even at 200 °C but treatment of this compound with Tf<sub>2</sub>O–DMAP (5:3 molar ratio w.r.t. **1**) at 0–

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

The capacity of Tf<sub>2</sub>O–DMAP to achieve clean cyclisation of systems possessing sensitive functionality is exemplified by the results shown in entries 2–4. Thus, compounds **3<sup>3d</sup>** and **5<sup>3d</sup>** undergo conversion into 2-deoxylycoricidine diacetate **4<sup>3d</sup>** and the pancratistatin analogue **6<sup>3d</sup>** respectively, on treatment with Tf<sub>2</sub>O–DMAP.† Attempts to effect the same conversions with POCl<sub>3</sub> only resulted in extensive decomposition of the substrates. Reaction of carbamate **7<sup>3a</sup>** with Tf<sub>2</sub>O–DMAP (at 0 °C for 2 h) gave the lactam **8** (85%) (mp 148–151 °C; lit.<sup>6</sup> mp 144–147 °C) while POCl<sub>3</sub>-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.<sup>7</sup> 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**<sup>6,8</sup> and oxoassoanine **12**.<sup>5a,8b,8f,9</sup> These natural products have been the subject of a number of synthetic studies<sup>5a,6,8,9</sup> largely because of their interesting biological activities.<sup>4</sup> 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**<sup>10</sup> was subjected to Suzuki cross-coupling<sup>11</sup> with arylboronic acid **17a**.<sup>3,12</sup> The double bond in the resulting biaryl **18a**† (99%) (mp 119–121 °C) was then removed by ionic hydrogenation<sup>13</sup> and the corresponding dihydro-compound **19a** (83%) thereby obtained. Finally, dihydroindole **19a** was converted into the carbamate **9** (90%) (mp



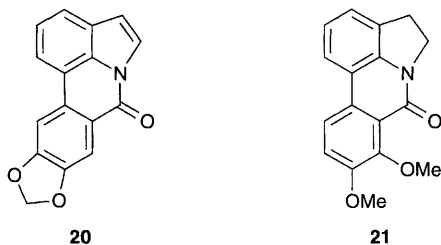
**Scheme 1** Reagents and conditions: i, Pd(PPh<sub>3</sub>)<sub>4</sub>, toluene, EtOH, sat. aq. Na<sub>2</sub>CO<sub>3</sub>, reflux, 4 d; ii, NaCNBH<sub>3</sub>, AcOH, 15 °C, 2 h; iii, NaH, ClCO<sub>2</sub>Me, THF, 15 °C, 16 h

102–104 °C) by reaction with methyl chloroformate and sodium hydride. While POCl<sub>3</sub> failed to effect cyclisation, treatment of substrate **9** with Tf<sub>2</sub>O–DMAP (entry 5, Table 1) gave

anhydrolycorinone **10**<sup>6,8</sup> in 88% yield. § 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) promoted dehydrogenation<sup>8c</sup> of compound **10** resulted in the efficient (71%) formation of the

**Table 1** Tf<sub>2</sub>O–DMAP-promoted Bischler–Napieralski cyclisation reactions.

Entry	Substrate	Cyclisation product	Yield (%)	Result with POCl <sub>3</sub>
1			92	No reaction
2			85	Complex mixtures
3			60	Complex mixtures
4			85	<b>8</b> (46%) + <b>15</b>
5			<b>10</b> (88%) ----- <b>12</b> (76%)	(46%) No Reaction
6			+ <b>21</b> (7%)	
7			78	<b>14</b> (60%)



alkaloid hippadine **20**<sup>8b-f,14</sup> (mp 216–218 °C; lit.<sup>14c</sup> 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 **17b**<sup>15</sup> 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.<sup>9b</sup> mp 276–277 °C) together with regioisomer **21** (7%) (mp 162–164 °C).

The Tf<sub>2</sub>O–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**<sup>16</sup> is readily converted into the tetracycle **14** (78%) (mp 199–201 °C; lit.<sup>16</sup> mp 198–202 °C) on treatment with Tf<sub>2</sub>O–DMAP and the structure of the product has been confirmed by X-ray analysis.¶ While the same conversion can be effected with POCl<sub>3</sub> a lower yield (60%) of an impure product is obtained.<sup>16</sup>

We acknowledge financial support from the Australian Research Council in the form of a research grant to M. G. B. and an APRA Scholarship to C. J. C.; A. W. is the grateful recipient of a University of Melbourne Post-Graduate Scholarship. S. B. thanks the Swiss National Science Foundation for the award of a Post-Doctoral Fellowship.

Received, 17th July 1995; Com. 5/04696C

## 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 reacylation 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<sup>-3</sup> solution of Tf<sub>2</sub>O (1.05 ml, 1.16 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> 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 CH<sub>2</sub>Cl<sub>2</sub> (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 CH<sub>2</sub>Cl<sub>2</sub> (10 ml), washed with saturated aqueous Na<sub>2</sub>CO<sub>3</sub> (1 × 5 ml), 20% v/v aqueous acetic acid (1 × 5 ml) and then saturated aqueous Na<sub>2</sub>CO<sub>3</sub> (1 × 5 ml) before being dried over Na<sub>2</sub>SO<sub>4</sub>. 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.<sup>8f</sup> 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<sub>f</sub> 0.5) was extracted (CHCl<sub>3</sub>) 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 Na<sub>2</sub>CO<sub>3</sub> wash described in the above work-up are omitted. The required isoquinoline and 4-(N,N-dimethylamino)pyridine are then separated from one another by chromatography on alumina.

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

## References

- G. Fodor and S. Nagubandi, *Tetrahedron*, 1980, **36**, 1279.
- S. Nagubandi and G. Fodor, *Heterocycles*, 1981, **15**, 165. For related efforts concerning the Ritter and Vilsmeier–Haack reactions see: A. García-Martínez, 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.
- (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.
- 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.
- 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.
- D. B. Grotjahn and K. P. C. Vollhardt, *Synthesis*, 1993, 579.
- H. Iida, S. Aoyagi and C. Kibayashi, *J. Chem. Soc., Perkin Trans. 1*, 1975, 2502.
- 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.
- 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.
- G. Bartoli, G. Palmieri, M. Bosco and R. Dalpozzo, *Tetrahedron Lett.*, 1989, **30**, 16.
- G. M. Carrera and G. S. Sheppard, *Synlett.*, 1994, 93.
- E. M. Campi, W. R. Jackson, S. M. Marcuccio and C. G. M. Naeslund, *J. Chem. Soc., Chem. Commun.*, 1994, 2395.
- G. Gribble and J. Hoffmann, *Synthesis*, 1977, 859.
- 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.
- R. B. Miller and J. J. Svoboda, *Synth. Commun.*, 1994, **24**, 1187.
- M.-A. Siegfried, H. Hilpert, M. Rey and A. S. Dreiding, *Helv. Chim. Acta*, 1980, **63**, 938.