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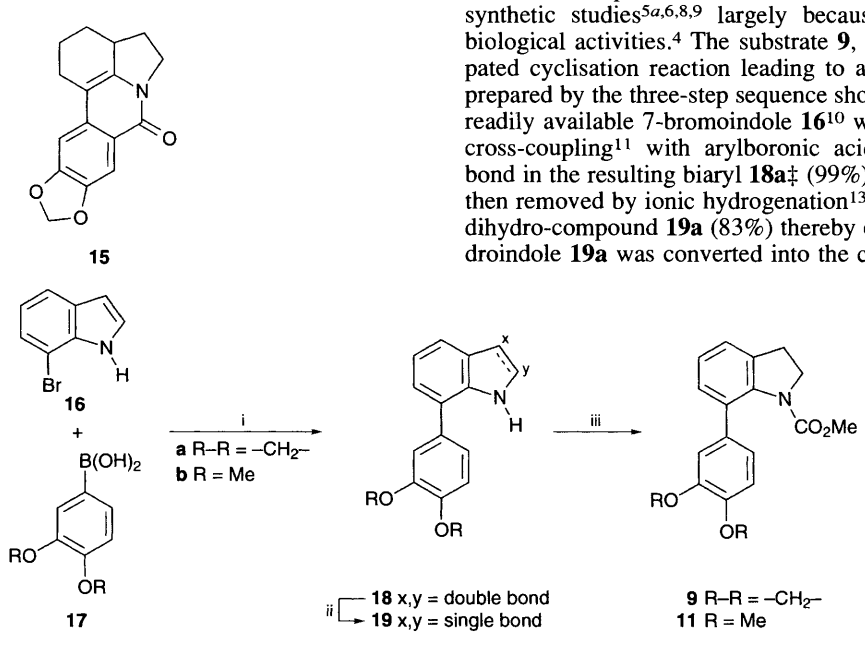
A combination of triflic anhydride and 4-(*N,N*-dimethylamino)pyridine effects Bischler–Napieralski cyclisation of β-phenethylcarbamates and β-phenethylamides under very mild conditions.

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 ($POCl_3$). Consequently, substrates containing sensitive functionality often do not survive these conditions. This situation has prompted efforts[2] 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[3] directed towards the synthesis of various *Amaryllidaceae* alkaloids,[4] we have discovered that a combination of trifluoromethanesulfonic (triflic) anhydride (Tf_2O) 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 $POCl_3$ 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 **1**[3b] does not react with $POCl_3$ even at 200 °C but treatment of this compound with Tf_2O–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**[3b,5] in 92% yield. The success of such reactions was critically dependent upon the molar ratios of Tf_2O and DMAP employed. The most favourable conditions uncovered so far require *ca.* 5 molar equivalents (w.r.t. substrate) of Tf_2O and *ca.* 3 molar equivalents of DMAP. Employing an excess of Tf_2O w.r.t. DMAP appears to be essential since using the two reagents in equimolar amounts is ineffective. Furthermore, Tf_2O alone fails to achieve clean cyclisation.

The capacity of Tf_2O–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 Tf_2O–DMAP.† Attempts to effect the same conversions with $POCl_3$ only resulted in extensive decomposition of the substrates. Reaction of carbamate **7**[3a] with Tf_2O–DMAP (at 0 °C for 2 h) gave the lactam **8** (85%) (mp 148–151 °C; lit.[6] mp 144–147 °C) while $POCl_3$-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.

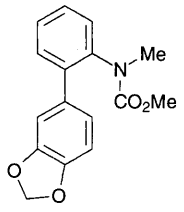
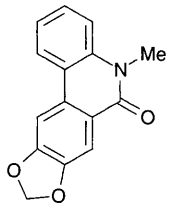
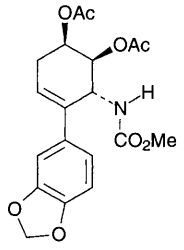
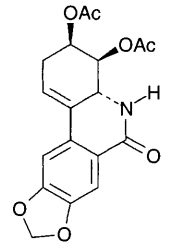
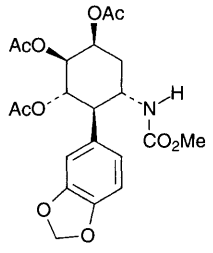
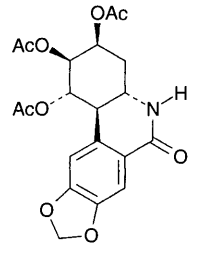
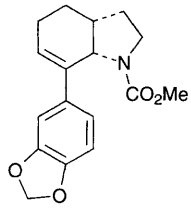
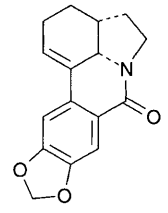
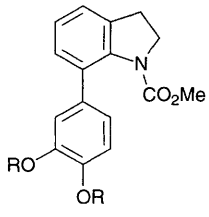
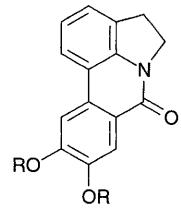
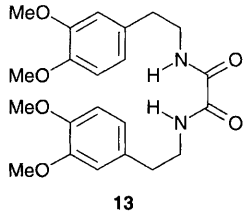
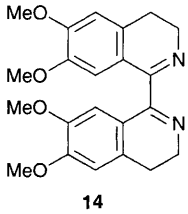
The discovery of new and mild conditions for effecting Bischler–Napieralski cyclisation has allowed the development of abbreviated syntheses of the pyrrolophenanthridinone alkaloids anhydrolycorinone **10**[6,8] and oxoassoanine **12**.[5a,8b,8f,9] These natural products have been the subject of a number 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-coupling[11] with arylboronic acid **17a**.[3,12] The double bond in the resulting biaryl **18a**‡ (99%) (mp 119–121 °C) was then removed by ionic hydrogenation[13] and the corresponding dihydro-compound **19a** (83%) thereby obtained. Finally, dihydroindole **19a** was converted into the carbamate **9** (90%) (mp

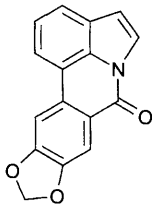


Scheme 1 *Reagents and conditions*: i, $Pd(PPh_3)_4$, toluene, EtOH, sat. aq. Na_2CO_3, reflux, 4 d; ii, $NaCNBH_3$, AcOH, 15 °C, 2 h; iii, NaH, $ClCO_2Me$, THF, 15 °C, 16 h

102–104 °C) by reaction with methyl chloroformate and sodium *hydride*. While $POCl_3$ 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 dehydrogenation[8c] of compound **10** resulted in the efficient (71%) formation of the

Table 1 Tf_2O–DMAP-promoted Bischler–Napieralski cyclisation reactions.

Entry	Substrate	Cyclisation product	Yield (%)	Result with $POCl_3$
1	 **1**	 **2**	92	No reaction
2	 **3**	 **4**	85	Complex mixtures
3	 **5**	 **6**	60	Complex mixtures
4	 **7**	 **8**	85	**8** (46%) + **15**
5 R–R = $-CH_2-$	 **9** R–R = $-CH_2-$	 **10** R–R = $-CH_2-$	**10** (88%)	(46%)
6 R = Me	**11** R = Me	**12** R = Me	---------- **12** (76%) + **21** (7%)	No Reaction
7	 **13**	 **14**	78	**14** (60%)



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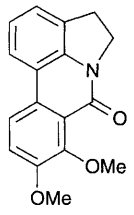

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alkaloid hippadine **20**[8b–f,14] (mp 216–218 °C; lit.[14c] mp 215–217 °C).

The synthesis of oxoassoanine **12** followed along similar lines to those used in the preparation of congener **10**. Thus, boronic acid **17b**[15] 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 Tf_2O–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 Tf_2O–DMAP and the structure of the product has been confirmed by X-ray analysis.¶ While the same conversion can be effected with $POCl_3$ 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 Tf_2O (1.05 ml, 1.16 mmol) in anhydrous CH_2Cl_2 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_2Cl_2 (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_2Cl_2 (10 ml), washed with saturated aqueous Na_2CO_3 (1 × 5 ml), 20 % *v/v* aqueous acetic acid (1 × 5 ml) and then saturated aqueous Na_2CO_3 (1 × 5 ml) before being dried over Na_2SO_4. 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.[8f] 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 ($CHCl_3$) 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_2CO_3 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 been deposited with the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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