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A Versatile Cyclodehydration Reaction for the Synthesis of Isoquinoline and β-Carboline Derivatives

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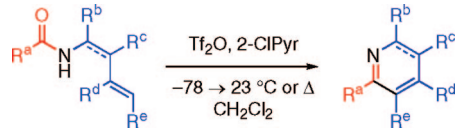
ABSTRACT



The direct conversion of various amides to isoquinoline and β-carboline derivatives via mild electrophilic amide activation, with trifluoromethanesulfonic anhydride in the presence of 2-chloropyridine, is described. Low-temperature amide activation followed by cyclodehydration upon warming provides the desired products with short overall reaction times. The successful use of nonactivated and halogenated phenethylene derived amides, *N*-vinyl amides, and optically active substrates is noteworthy.

The venerable Bischler−Napieralski reaction offers an important strategy for the synthesis of various azaheterocycles.[1,2] Isoquinolines and β-carbolines, including their reduced derivatives, can be found as substructures in many important natural products, pharmaceuticals, and other fine chemicals.[3] We have reported the syntheses of pyridine[4a] and pyrimidine[4b] derivatives via the intermolecular condensation of readily available *N*-vinyl- and *N*-arylamides[5] with various nucleophiles. Herein we report mild reaction conditions for the Bischler−Napieralski based synthesis of isoquinoline and β-carboline derivatives from readily available amides.

During our studies concerning the syntheses of pyridines and quinolines via an intermolecular condensation reaction,[4b] we observed a competitive intramolecular cyclization reaction in a single case where a Morgan−Walls[6] cyclization pathway was possible. *N*-Phenethylbenzamide (**1**, Table 1) was used to further investigate this intramolecular condensation reaction. Consistent with our observations on amide activation for the intermolecular addition of σ- or π-nucleophiles,[4] the use of trifluoromethanesulfonic anhydride (Tf_2O)[7] and 2-chloropyridine[8] (2-ClPyr) as the base additive were found to be

(1) (a) Bischler, A.; Napieralski, B. *Ber.* **1893**, *26*, 1903. (b) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74.

(2) For representative reports, see: (a) Tóth, J.; Nedves, A.; Dancsó, A.; Blaskó, G.; Töke, L; Nyerges, M. *Synthesis* **2007**, 1003. (b) Spaggiari, A.; Davoli, P.; Blaszczak, L. C.; Prati, F. *Synlett* **2005**, 661. (c) Banwell, M. G.; Bissett, B. D.; Busato, S.; Cowden, C. J.; Hockless, D. C. R.; Holman, J. W.; Read, R. W.; Wu, A. W. *J. Chem. Soc., Chem. Commun.* **1995**, 2551. (d) Larsen, R. D.; Reamer, R. A.; Corley, E. G.; Davis, P.; Grabowski, E. J. J.; Reider, P. J.; Shinkai, I. *J. Org. Chem.* **1991**, *56*, 6034. (e) Hendrickson, J. B.; Schwartzman, S. M. *Tetrahedron Lett.* **1975**, *16*, 277.

(3) For reviews on isoquinolines and their reduced derivatives, see: (a) Jones, G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., McKillop, A., Eds.; Pergamon: Oxford, 1996; Vol. 5, p 167. (b) Bentley, K. W. *Nat. Prod. Rep.* **2006**, *23*, 444. (c) Kartsev, V. G. *Med. Chem. Res.* **2004**, *13*, 325. (d) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341. (e) Joule, J. A.; Mills, K. In *Heterocyclic Chemistry*, 4th ed.; Blackwell Science Ltd.: Cambridge MA, 2000; p 121. (f) Rozwadowska, M. D. *Heterocycles* **1994**, *39*, 903. For a review on β-carbolines and their reduced derivatives, see: (g) Love, B. E. *Org. Prep. Proced. Int.* **1996**, *28*, 3.

(4) (a) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 14254. (b) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096.

(5) For recent advances in synthesis of *N*-vinyl- and *N*-arylamides, see: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; p 1051. (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (d) Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, 973.

(6) (a) Morgan, G. T.; Walls, L. P. *J. Chem. Soc.* **1931**, 2447. (b) Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2007**, *72*, 7720. (c) Hutchinson, I.; Stevens, M. F. G. *Org. Biomol. Chem.* **2007**, *5*, 114.

(7) (a) For an elegant prior report on amide activation, see: Charette, A. B.; Grenon, M. *Can. J. Chem.* **2001**, *79*, 1694. (b) Review: Baraznenok, I. L.; Nenajdenko, V. G.; Balenkova, E. S. *Tetrahedron* **2000**, *56*, 3077.

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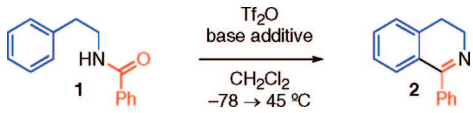
Table 1. Selection of Base Additive[a]



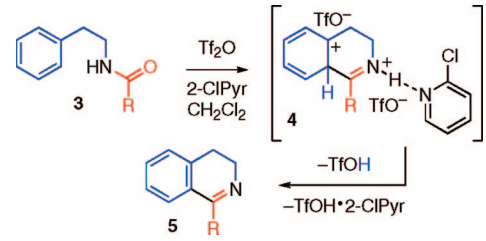
entry	base additive	equiv	isolated yield (%)
1	Et_3N	1.2	18
2	pyridine	1.2	65
3	ethyl nicotinate	1.2	51
4	2-bromopyridine	1.2	74
5	2-fluoropyridine	1.2	90
6	3-chloropyridine	1.2	79
7	2-chloropyridine	1.2	95
8	2-chloropyridine	0	43
9	2-chloropyridine	2.0	91

[a] Reaction conditions: Tf_2O (1.1 equiv), CH_2Cl_2, 45 °C, 2 h.

optimal for a mild cyclodehydration reaction to provide the desired 3,4-dihydroisoquinoline **2** in 95% yield (Table 1, entry 7). The reaction was found to be less sensitive to superstoichiometric quantities of 2-ClPyr as compared to its absence (compare entries 7−9, Table 1), allowing the inclusion of excess base additive for Brønsted acid-sensitive substrates.[9] Electrophilic amide activation[10] followed by intramolecular π-nucleophilic cyclization and subsequent deprotonation directly provides the desired product **5** (Scheme 1).

A wide range of *N*-phenethylamide derivatives were found to readily provide the corresponding 3,4-dihydroisoquinoline

Scheme 1. Intramolecular Dehydrative Cyclization



products (Figure 1, **2**, **6**−**14**). Alkoxy and unsubstituted *N*-phenethylamides provided the desired dihydroisoquinoline products at ambient temperature or with mild heating. The conversion of recalcitrant substrates was found to be optimal via short (5 min) microwave irradiation.[11] For example, deactivated halogenated *N*-phenethylamides did not cyclize at ambient temperature but provided the desired 3,4-dihydroisoquinolines with microwave irradiation (Figure 1, **9** and **10**). The formation of the phenylalaninol-derived dihydroisoquinoline **14** was noted to occur with no loss in optical activity.[12] Significantly, sensitive *N*-vinylamides[13] were used as substrates in this chemistry to directly provide isoquinoline derivatives (Figure 1, **15**−**18**). While (*E*)-*N*-styrylcyclohexanecarboxamide did not provide isoquinoline **15**, (*Z*)-*N*-styrylcyclohexanecarboxamide was converted to the desired isoquinoline **15** in moderate yield (Figure 1). It should be noted that this substrate was sensitive (vide infra) to decomposition/polymerization following electrophilic amide activation. Tri- and tetrasubstituted enamides proved

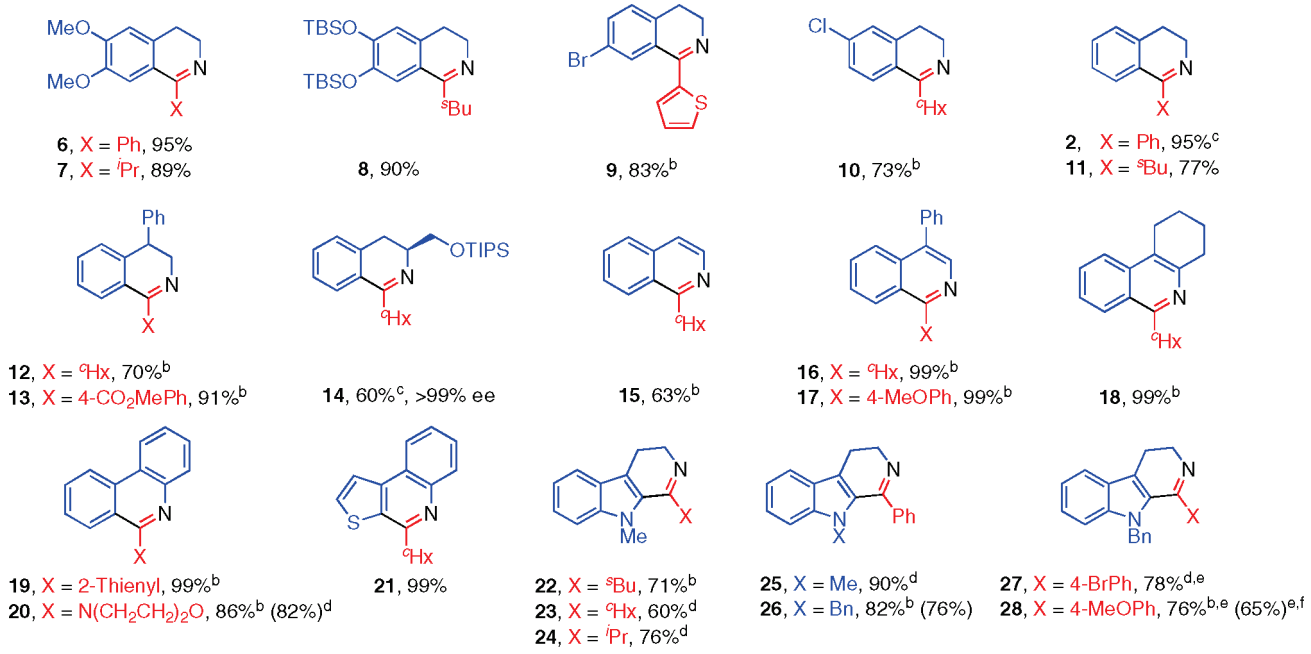
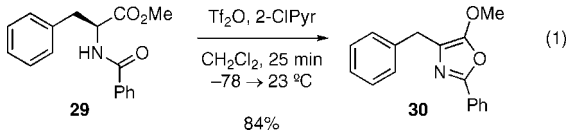


Figure 1. Synthesis of isoquinoline and β-carboline derivatives. [a]Average of two experiments. Uniform reaction conditions unless otherwise noted: Tf_2O (1.1 equiv), 2-ClPyr (1.2 equiv), CH_2Cl_2, −78 → 23 °C, 1 h. [b]−78 → 140 °C, 5 min. [c]−78 → 45 °C, 2 h. [d]−78 → 23 °C, 2 h. [e]Tf_2O (1.0 equiv). [f]−78 → 23 °C, 6 h.

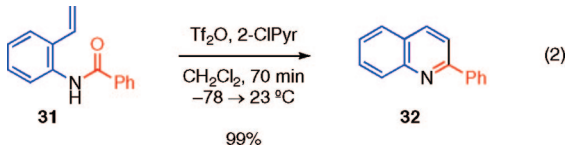
to be excellent substrates for this chemistry and efficiently gave the corresponding azaheterocycles (Figure 1, **16**−**18**). *o*-Arylaniline-derived amides afforded the desired fused tricyclic azaheterocycles, reminiscent of Morgan−Walls cyclization products, in good yield (Figure 1, **19**−**21**). Additionally, the use of tryptamine-derived substrates, optimally *N*-alkyl derivatives, gave the corresponding 3,4-dihydro-β-carbolines (Figure 1, **22**−**28**).

Highly deactivated substrates such as *N*-(4-nitrophenethyl)cyclohexanecarboxamide or *N*-(4-(trifluoromethyl)-phenethyl)benzamide did not provide the corresponding dihydroisoquinolines.[14] This is likely due to a more rapid rate of elimination/decomposition upon activation as compared to the desired cyclodehydration reaction. Tryptamine-derived amides bearing a sulfonyl group on the indolyl nitrogen were not substrates for this chemistry, and unsubstituted indole derivatives led to rapid indolyl nitrogen *N*-sulfonylation of the starting material under the reaction conditions. It should be noted that in some cases minor side products resulting from oxidation (vide infra) of 3,4-dihydro-β-carboline were observed.[15] Additionally, using the phenylalanine derivative **29** as a substrate under the standard reaction conditions competitively gave the oxazole **30** in 84% yield (eq 1).[16,17]



(1)

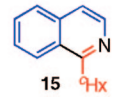
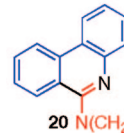
When 2-vinylaniline-derived amide **31** was exposed to the standard cyclodehydration reaction conditions described above, a highly efficient condensation reaction ensued to afford 2-phenylquinoline (**32**, eq 2) in 99% isolated yield.



(2)

The direct comparison of the herein described condensation reaction with related protocols further highlights the advantages offered by this chemistry (Table 2).[2] The synthesis of 3,4-dihydroisoquinoline **2**, isoquinoline **15**, and phenanthridine **20** is illustrative. Synthesis of 3,4-dihydroisoquinoline **2** was found to be most efficient using the conditions described here as compared to other reported condensation reaction conditions (Table 2). Sensitive substrates, such as the acid-sensitive (*Z*)-*N*-styrylcyclohexanecarboxamide, were found to be incompatible with the broadly used conditions involving phosphorus oxychloride ($POCl_3$) in conjunction with heating.[2a] Similarly, the use of reaction conditions employing oxalyl chloride and iron trichloride did not provide the desired phenanthridine **20** from the corresponding urea substrate.[2d]

Table 2. Direct Comparison of Condensation Reaction Conditions

	reaction conditions			
product	Tf_2O (1.2 equiv) 2-ClPyr (*This work*)[a]	$POCl_3$ (3.0 equiv) (*Ref 2a*)[b]	Oxalyl Chloride (1.1 equiv) $FeCl_3$ (*Ref 2d*)[c]	Tf_2O (5.0 equiv) DMAP (*Ref 2c*)[d]
 **2**	95%	23%	15%	71%
 **15**	63%	0%	9%	42%
 **20**	86%	10%	0%	63%

[a] See Figure 1 for reaction conditions. [b] $POCl_3$ (3.0 equiv), xylenes, 150 °C, 3 h. [c] (1) Oxalyl chloride (1.1 equiv); $FeCl_3$ (1.2 equiv), CH_2Cl_2, 23 °C, 12 h. (2) MeOH−H_2SO_4 (19:1), 65 °C, 1 h. [d] Tf_2O (5.0 equiv), DMAP (3.0 equiv), CH_2Cl_2, 23 °C, 16 h.

While in all three cases (Table 2) the use of superstoichiometric Tf_2O in conjunction with 4-(dimethylamino)-pyridine (DMAP) provided the desired product,[2c] the competing oxidation reaction in more sensitive substrates is a potential complication. For example, using the herein described conditions, electrophilic activation of amide **33** (eq 3, 97% ee) afforded the desired optically active 3,4-dihydroisoquinoline **34** in 87% yield and 90% ee without undesired oxidation to the corresponding isoquinoline.[18] However, electrophilic activation of amide **33** using the

(8) (a) Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 6072. (b) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269.

(9) The inhibitory effect of excess 2-ClPyr is more pronounced when using weak σ-nucleophiles (i.e., nitriles, see ref 4a) as compared to stronger nucleophiles (i.e., ynamines, see ref 4b).

(10) Electrophilic activation of *N*-alkylamides may lead to a transient highly electrophilic nitrilium ion (or a pyridinium adduct) that is trapped by the arene ring.

(11) Amide activation at ambient temperature under standard conditions generally led to the desired product; however, reaction times were often significantly shortened and isolated yields often increased upon heating.

(12) See the Supporting Information for details.

(13) For representative preparation of enamides, see: Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667, and ref 5.

(14) The use of *N*-(4-nitrophenethyl)cyclohexanecarboxamide as substrate provided 1-nitro-4-vinylbenzene as the major product.

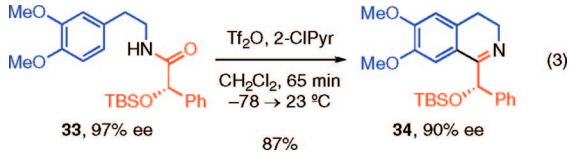
(15) For example, **27** and **28** were isolated along with **36** (12%, Figure 2) and **35** (6%, Figure 2), respectively. Additionally, minor *N*-trifluoromethanesulfonylated spirocyclic byproducts were detected.

(16) For competitive oxazole formation under the Bischler−Napieralski reaction conditions, see: Liu, Z. Z.; Tang, Y. F.; Chen, S. Z. *Chin. Chem. Lett.* **2001**, *12*, 947.

(17) While the desired 3,4-dihydroisoquinoline **14** (Figure 1) was prepared from the corresponding *O*-triisopropylsilyl phenylalaninol derived amide, the use of the nonsilylated substrate (*S*)-*N*-(1-hydroxy-3-phenylpropan-2-yl)cyclohexanecarboxamide led to competitive oxazoline formation. For a related report, see: Whelligan, D. K.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 4609.

(18) Epimerization of 3,4-dihydroisoquinoline **34** can occur within 1 h at room temperature in CH_2Cl_2 (0.3 M) or when stored neat, highlighting the sensitivity of the product.

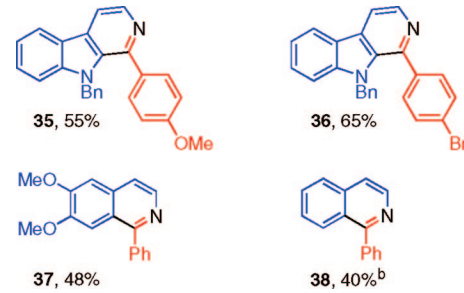
reported reaction conditions[2c] employing excess Tf_2O−DMAP gave the desired product **34** in 31% yield, and with only 63% ee, in addition to 26% yield of the corresponding isoquinoline derivative due to oxidation of **34**. Additionally, activation of amide **33** via the typical condensation reaction conditions employing $POCl_3$ failed to provide the desired product **34** due to competitive decomposition.



33, 97% ee — 87% — **34**, 90% ee

As mentioned the 3,4-dihydro-β-carboline condensation products are subject to oxidation with Tf_2O, affording the corresponding β-carbolines.[15,19] In the case of 3,4-dihydroisoquinoline **34** this was a significant complication when excess Tf_2O was used (vide supra). Indeed, exposure of azaheterocycles **2**, **6**, and **27**−**28** to Tf_2O and 2-ClPyr resulted in the corresponding oxidation products (Figure 2). Electron-rich dihydro-β-carbolines are more sensitive to this oxidation reaction as compared to dihydroisoquinolines (Figure 2). For comparison, while oxidation of 3,4-dihydroisoquinoline **2** to isoquinoline **38** required excess reagents and heating to 140 °C, the oxidation of 3,4-dihydro-β-carboline **27** at 23 °C gave β-carboline **36** in 65% yield within 2 h (Figure 2).[20]

The chemistry described herein provides an efficient modified Bischler−Napieralski cyclodehydration reaction to access isoquinolines, β-carbolines, and their 3,4-dihydro derivatives. The successful use of unactivated, halogenated *N*-phenethylamides, sensitive *N*-vinylamides, and optically active substrates is noteworthy. The direct comparison of this chemistry with existing methods as shown in Table 2 and the observations discussed regarding epimerization and oxidation challenges in the context of substrate **33** highlight the advantages offered by this methodology.



35, 55% — **36**, 65% — **37**, 48% — **38**, 40%[b]

Figure 2. Tf_2O−2-ClPyr-promoted oxidation of 3,4-dihydro-β-carbolines and 3,4-dihydroisoquinolines. [a]Reaction conditions: Tf_2O (1.1 equiv), 2-ClPyr (1.2 equiv), CH_2Cl_2, −78 → 23 °C, 2 h. [b]Tf_2O (2.1 equiv), 2-ClPyr (2.2 equiv), CH_2Cl_2, −78 → 140 °C, 5 min.

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Supporting Information Available: Experimental procedures and spectroscopic data for **2**, **6**−**28**, **30**, **32**, and **34**−**38**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) For related oxidation reactions, see: (a) Spath, E.; Lederer, E. *Chem. Ber.* **1930**, *63B*, 120. (b) Hufford, C. D.; Sharma, A. S.; Oguntimein, B. O. *J. Pharm. Sci.* **1980**, *69*, 1180. (c) McMahon, R. M.; Thornber, C. W.; Ruchirawat, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2163. (d) Hilger, C. S.; Fugmann, B.; Steglich, W. *Tetrahedron Lett.* **1985**, *26*, 5975. (e) Andreu, I.; Cabedo, N.; Atassi, G.; Pierre, A.; Caignard, D. H.; Renard, P.; Cortesa, D.; Bermejoa, A. *Tetrahedron Lett.* **2002**, *43*, 757, and references therein.

(20) Using the conditions described in Figure 2, 3,4-dihydro-β-carboline **28** was completely converted to product **35**, whereas oxidation of azaheterocycles **2**, **6**, and **27** gave the corresponding products (Figure 2) along with recovered starting material (8%, 30%, and 10%, respectively).