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Org Lett. Author manuscript; available in PMC 2009 August 21.

Published in final edited form as:
Org Lett. 2008 August 21; 10(16): 3485–3488. doi:10.1021/ol801264u.

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

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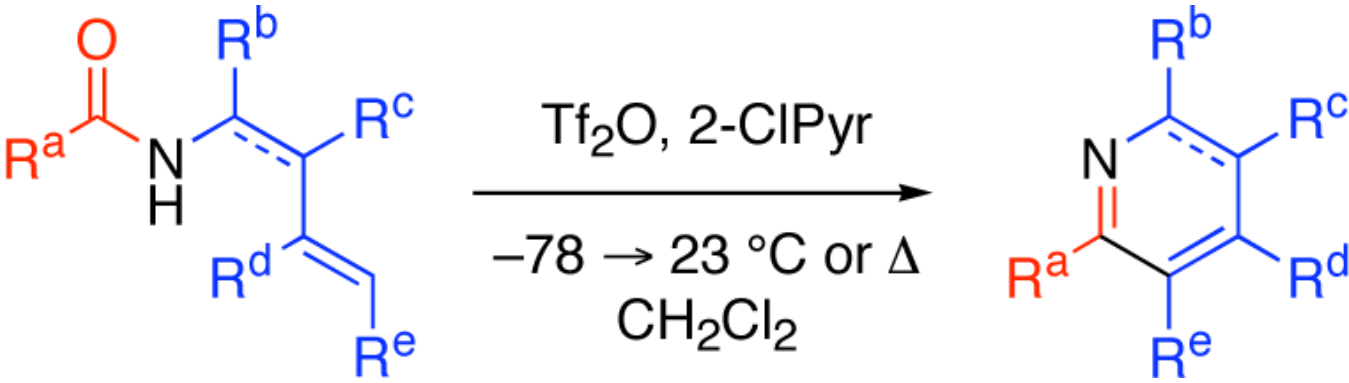
Abstract



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 non-activated and halogenated phenethylene derived amides, *N*-vinyl amides, and optically active substrates are 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*-aryl amides[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-

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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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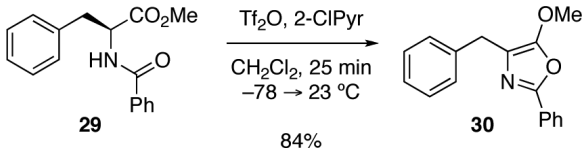
chloropyridine[8] (2-ClPyr) as the base additive were found to be optimal for a mild cyclodehydration reaction to provide the desired 3,4-dihydroisoquinoline **2** in 95% yield (Table 1, entry 7). The reaction was found to be less sensitive to superstoichiometric quantities of 2-ClPyr as compared to 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).

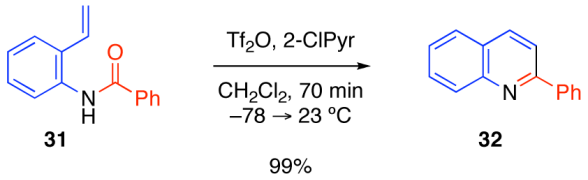
A wide range of *N*-phenethylamide derivatives were found to readily provide the corresponding 3,4-dihydroisoquinoline products (Figure 1, **2, 6**−**14**). Alkoxy and unsubstituted *N*-phenethylamides provided the desired dihydroisoquinoline products at ambient temperature or with mild heating. The 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*-vinyl amides[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 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 (Equation 1).[16,17]



(1)

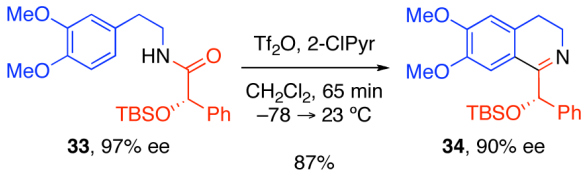
When 2-vinyl-aniline derived amide **31** was exposed to the standard cyclodehydration reaction conditions described above, a highly efficient condensation reaction ensued to afford 2-phenylquinoline (**32**, Equation 2) in 99% isolated yield.



(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]

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** (Equation 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 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.



(3)

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*-

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vinyl amides, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

M.M. is a Beckman Young Investigator and an Alfred P. Sloan research fellow. M.D.H. acknowledges an Amgen graduate fellowship. We acknowledge partial financial support by NIH-NIGMS (GM074825), NSF (547905), AstraZeneca, Amgen, Boehringer Ingelheim, GlaxoSmithKline, Lilly, and Merck.

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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*-alkyl amides 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 Supporting Information for details.
13. For representative preparation of enamides, see Jiang L, Job GE, Klapars A, Buchwald SL. Org. Lett 2003;5:3667. [PubMed: 14507200] and ref. 5.

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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*-triflouromethanesulfonylated spirocyclic byproducts were detected.

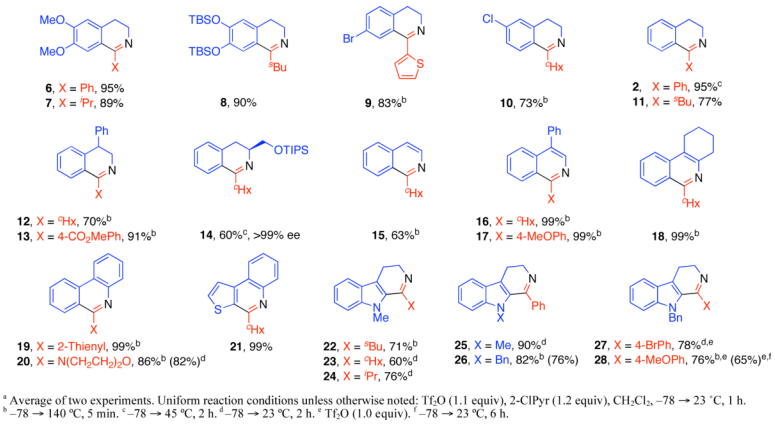
16. For competitive oxazole formation under the Bischler-Napieralski reaction conditions, see Liu ZZ, Tang YF, Chen SZ. Chin. Chem. Lett 2001;12:947.

17. While the desired 3,4-dihydroisoquinoline **14** (Figure 1) was prepared from the corresponding *O*-triisopropylsilyl phenylalaninol derived amide, the use of the non-silylated substrate (*S*)-*N*-(1-hydroxy-3-phenylpropan-2-yl)cyclohexanecarboxamide led to competitive oxazoline formation. For a related report, see Whelligan DK, Bolm C. J. Org. Chem 2006;71:4609. [PubMed: 16749795]

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

19. For related oxidation reactions, see: aSpath E, Lederer E. Chem. Ber 1930;63B:120.bHufford CD, Sharma AS, Oguntimein BO. J. Pharm. Sci 1980;69:1180. [PubMed: 7420287]cMcMahon RM, Thornber CW, Ruchirawat S. J. Chem. Soc., Perkin Trans. 1 1982:2163.dHilger CS, Fugmann B, Steglich W. Tetrahedron Lett 1985;26:5975.eAndreu I, Cabedo N, Atassi G, Pierre A, Caignard DH, 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%, 10%, respectively).



[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.

Figure 1.
Synthesis of isoquinoline and β-carboline derivatives.[a]

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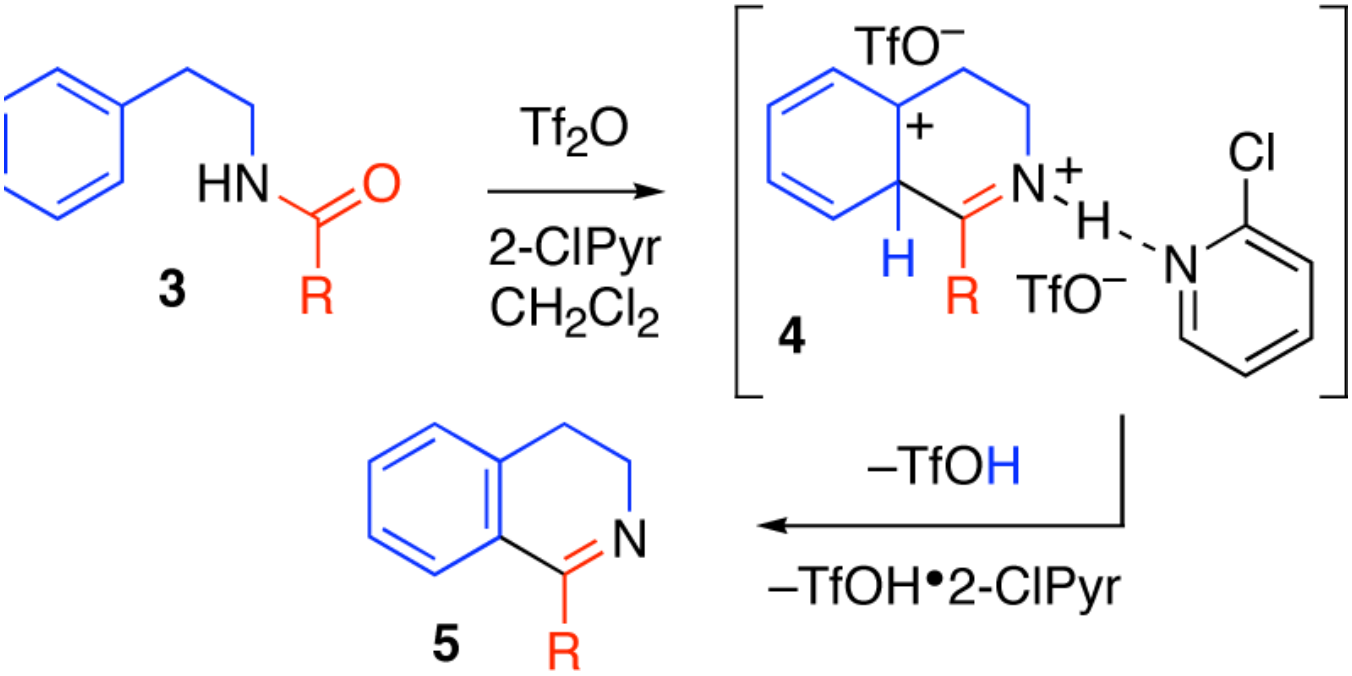

Scheme 1.
Intramolecular dehydrative cyclization.

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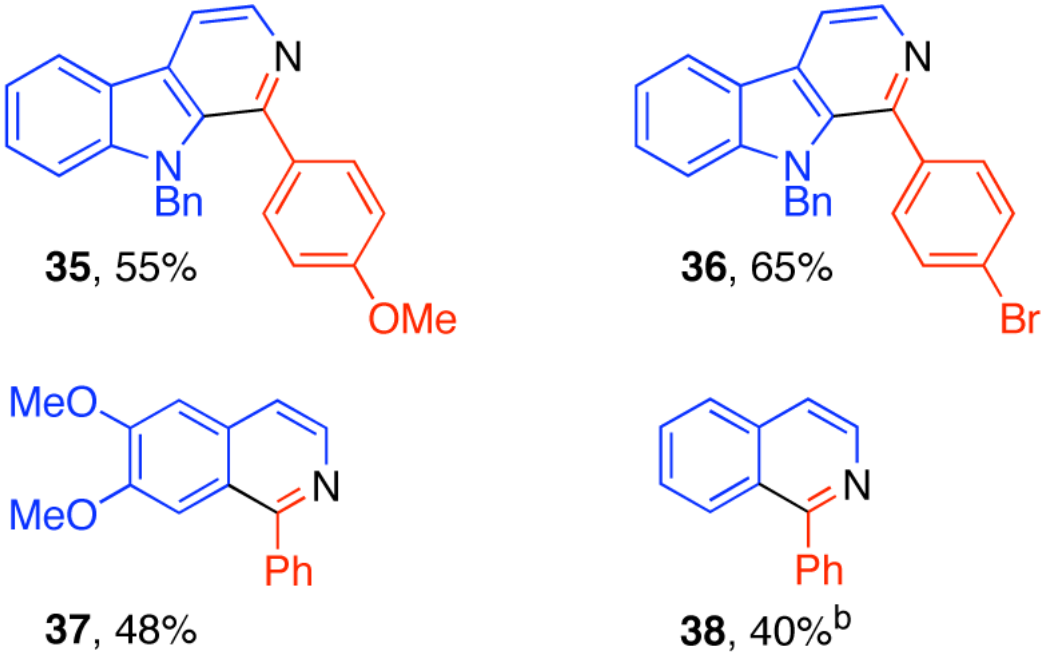

[a] Reaction conditions: Tf_2O (1.1 equiv), 2-ClPyr (1.2 equiv), CH_2Cl_2, –78 → 23 °C, 2 h. [b] Tf_2O (2.1 equiv), 2-ClPyr (2.2 equiv), CH_2Cl_2, –78 → 140 °C, 5 min.

Figure 2.
Tf_2O–2-ClPyr promoted oxidation of 3,4-dihydro-β-carbolines and 3,4-dihydroisoquinolines.[a]

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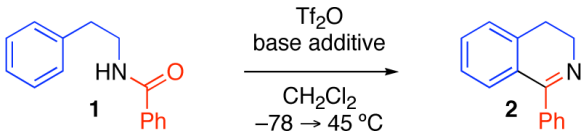
Table 1

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.

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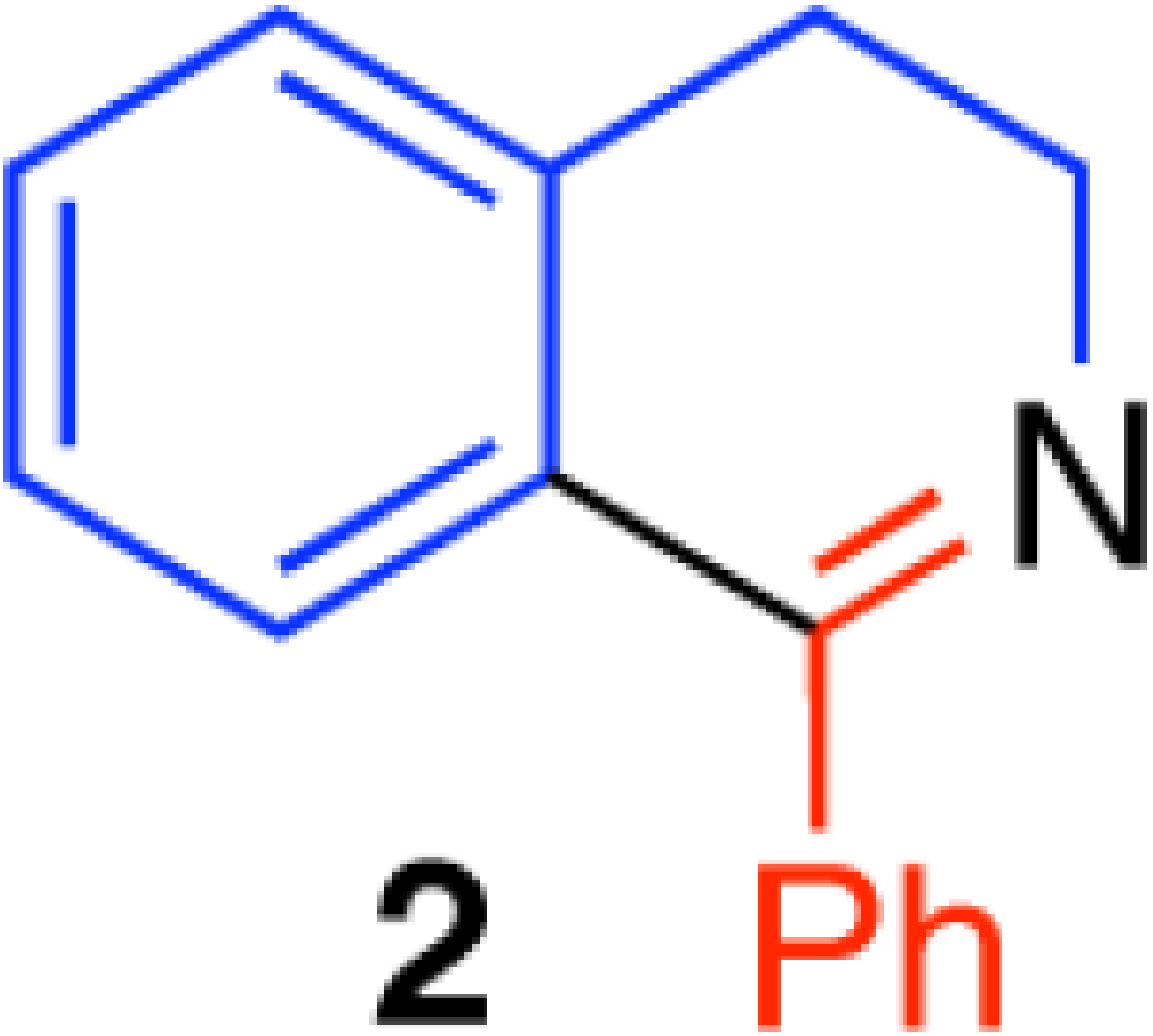
Table 2

Direct comparison of condensation reaction conditions.

product	Tf_2O (1.2 equiv) 2-ClPyr (*This work*) *a*	POC ec (*Re*
	95%	2

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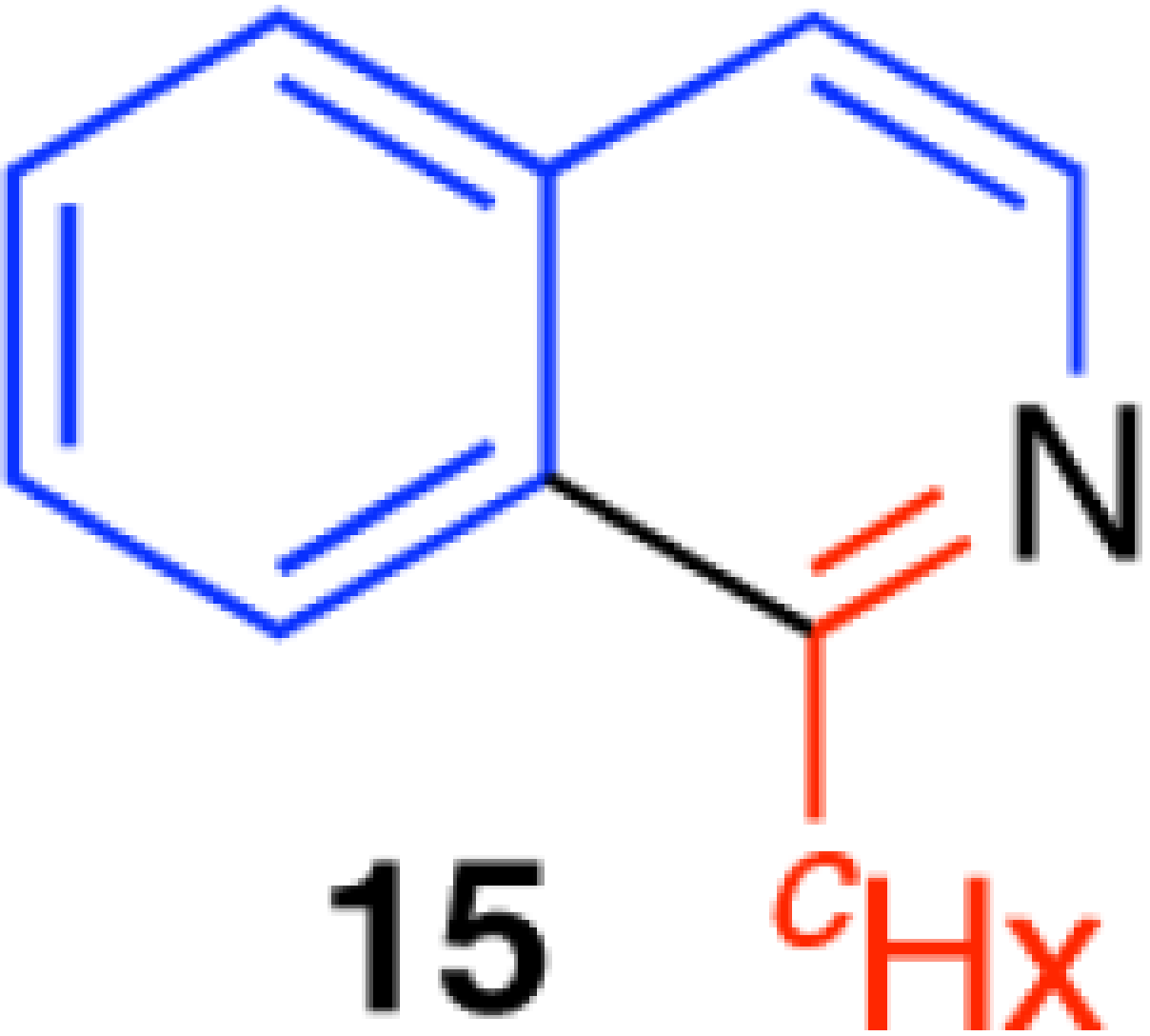
product	Tf_2O (1.2 equiv) 2-ClPyr (*This work*) [a]	POC ec (*Re*
	63%	

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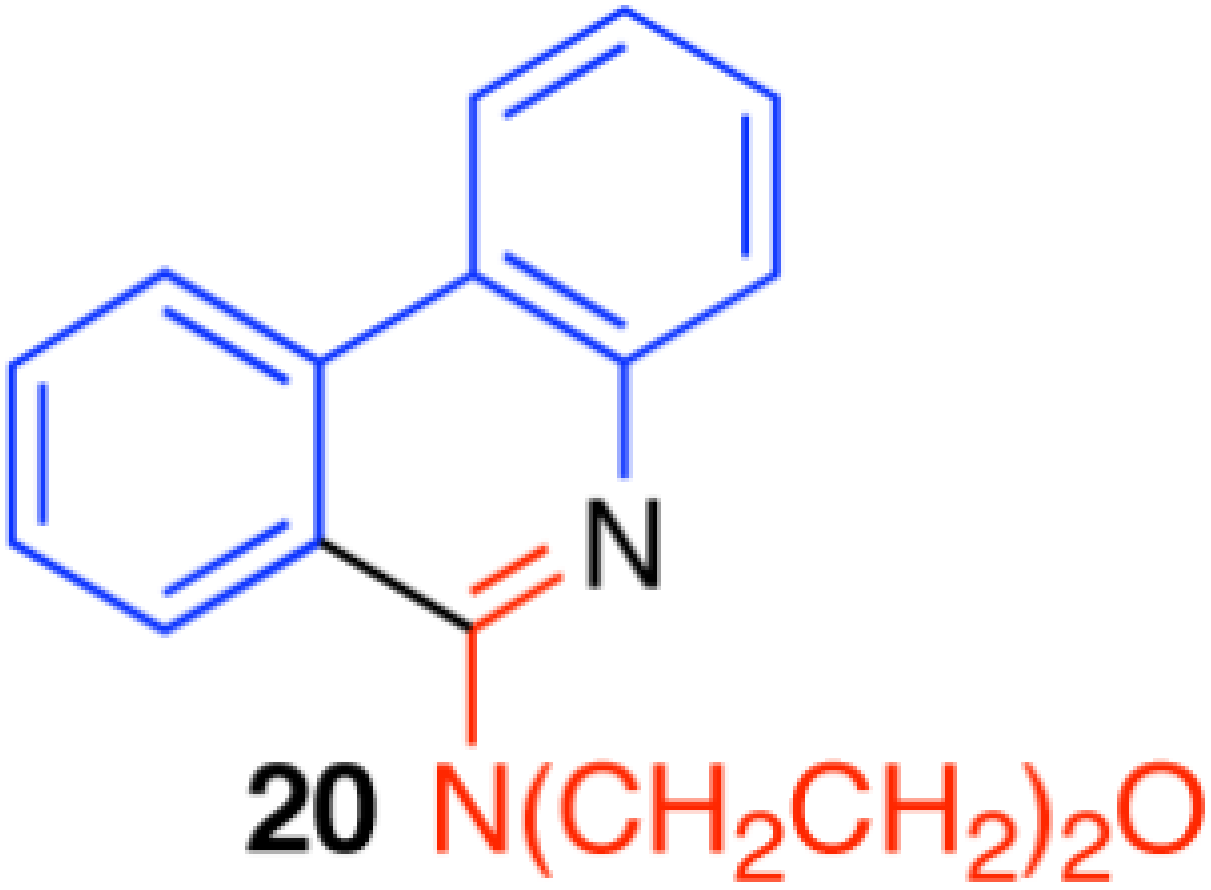
product	Tf_2O (1.2 equiv) 2-ClPyr (*This work*) [a]	POC ec (*Re*
 **20** $N(CH_2CH_2)_2O$	86%	1

[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.