A Very Mild Access to 3,4-Dihydroisoquinolines Using Triphenyl Phosphite–Bromine-Mediated Bischler–Napieralski-Type Cyclization

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This paper is dedicated to Albert Hofmann (1906–2008) in recognition of his pioneering work in the chemistry of mind-altering alkaloids.

Abstract: Substituted β-phenylethylamides undergo smooth intramolecular cyclization to 3,4-dihydroisoquinolines in good to excellent yields when treated with bromotriphenoxyphosphonium bromide at –60 °C in dichloromethane in the presence of triethylamine. The reaction proceeds under the mildest conditions ever reported for Bischler–Napieralski-type cyclizations. When chlorotriphenoxyphosphonium choride is used, low yields are obtained instead.

Key words: Bischler–Napieralski cyclization, phosphonium halides, iminoyl halides, isoquinoline alkaloids, necatorone, triphenyl phosphite

The isoquinoline skeleton features as the structural backbone in a plethora of alkaloids that occur typically, though by no means exclusively, in the plant kingdom, and which are endowed with a most impressive array of biological and pharmacological activities.[1,2]

Far back in 1893, Bischler and Napieralski paved the way to the synthesis of isoquinoline alkaloids by succeeding in preparing simple 3,4-dihydroisoquinolines by dehydration of β-phenylethylamides with either P_2O_5 or $ZnCl_2$ at temperatures above 250 °C.[3] Ever since, this reaction, which has been traditionally referred to as the Bischler–Napieralski cyclization,[4] has represented one of the most general methods for the construction of isoquinoline scaffolds en route to the total synthesis of natural alkaloids, in addition to the similarly useful and somewhat complementary Pictet–Spengler cyclization which, by contrast, is usually preferred when the 1,2,3,4-tetrahydroisoquinoline scaffold is desired instead.[5]

In the Bischler–Napieralski reaction, a suitable halogenating agent brings about the activation of the starting β-arylethylamide into an iminoyl chloride species which rearranges to a nitrilium ion intermediate that subsequently undergoes intramolecular electrophilic aromatic substitution.[6] In general, common reagents for the reaction are represented by $POCl_3$,[7] P_2O_5–$POCl_3$,[8] polyphosphoric acid–$POCl_3$,[9] P_2O_5–pyridine,[10] polyphosphate esters,[11] phosphonitrilic chloride,[12] as well as less conventional systems such as $POCl_3$ in ionic liquids[13] or acidic zeolites.[14] However, heating at reflux in toluene or, at the very best, acetonitrile, is always required. Although all these methods are operatively simple, the harsh reaction conditions may result detrimental, especially when sensitive functional groups are resident. To circumvent such limitations, milder reaction conditions under which Bischler–Napieralski-type cyclizations can be performed have also been developed. These include, for instance, triphosgene,[15] $(COCl)_2$/$FeCl_3$ in dichloromethane,[16] Ph_3P in refluxing CCl_4[17] or, in the case of 3,4-dihydroisoquinolones, Tf_2O/DMAP[18] or $AlCl_3$/KI.[19]

In the course of our studies on mild activation of amides using chlorotriphenoxyphosphonium chloride, viz. $(PhO)_3P^+ClCl^-(TPPCl_2)$,[20] indolamides were found to undergo efficient Bischler–Napieralski-type intramolecular cyclization, which allowed us to disclose a very mild and straightforward access to 3,4-dihydro-β-carbolines in good to excellent yields.[21] By contrast, when activated β-phenylethylamides were used, formation of the corresponding 3,4-dihydroisoquinolines proceeded only in poor yields.[21] Such a failure was attributed to the lower reactivity of the phenyl ring toward electrophilic substitution compared to the indole nucleus, and we surmised that an increase of the electrophilic character of the iminoyl halide intermediate would result in a more efficient cyclization to the desired 3,4-dihydroisoquinoline framework with much more satisfactory yields. As our own results on the dehydration of aromatic and aliphatic amides were meanwhile revealing a much higher reactivity of bromotriphenoxyphosphonium bromide, viz. $(PhO)_3P^+BrBr^-(TPPBr_2)$, with respect to $TPPCl_2$,[22] we felt that the same kind of triphenyl phosphite–bromine-based chemistry could be successfully extended to the cyclocondensation of β-phenylethylamides to 3,4-dihydroisoquinolines.

To put this plan into practice, a suitable set of variously substituted β-phenylethylamides was prepared. Amides **1a**–**h** were synthesized in multigram scale by standard acylation of the parent amine following well trodden paths.[23] When β-phenylethylamides **1a**–**h** were treated with a slight excess of freshly prepared $TPPBr_2$ at –60 °C in dichloromethane in the presence of triethylamine, the cyclization products **2a**–**h** were obtained in moderate to excellent yields (Scheme 1).

In a typical experiment, bromine is added to a solution of triphenyl phospite in anhydrous dichloromethane maintained at –60 °C under argon atmosphere. Triethylamine

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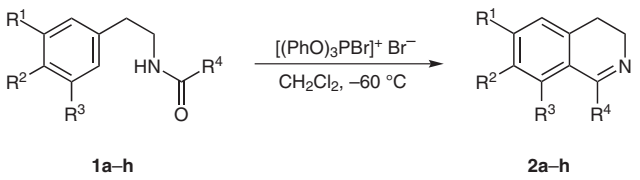

Scheme 1 $TPPBr_2$-promoted Bischler–Napieralski-type cyclization of β-phenylethylamides to 3,4-dihydroisoquinolines

and the amide are then added, and the mixture is gradually warmed to room temperature over a period of two hours, and left to stir overnight. The resulting 3,4-dihydroisoquinoline is recovered as free base after acid/base extraction, and no further chromatographic purification is required.[24] The cyclization results are summarized in Table 1.

Activated β-phenylethylamides **1c**–**h** (entries 3–8) afforded the corresponding 3,4-dihydroisoquinolines in good to excellent yields (62–92%). Results for homoveratrylamides **1e**–**g** (entries 5–7) are comparable, showing that the effect of different *N*-acyl groups on the cyclization is negligible, as already observed for Bischler–Napieralski cyclizations under classical conditions.[4b] Further increase in the ring substitution degree is likely to expose the aromatic ring to side reactions and may account for the slightly lower yield observed for the cyclization of *N*-acetyl mescaline **1h** (entry 8). By contrast, in the case of amides **1a** and **1b** (entries 1 and 2) where the cyclization is bound to occur either onto an inactivated phenyl ring or on ring positions which are not activated, respectively, yields are poor. With these inactivated substrates, $TPPCl_2$ failed to afford any cyclization product, and even in the case of activated β-phenylethylamides **1e** and **1h** the cyclization yields remained unsatisfactory, thereby limiting the usage of $TPPCl_2$ for the synthesis of 3,4-dihydroisoquinolines.

Of note, compound **2e** is dehydrosalsolidine, a plant alkaloid which occurs in the saguaro cactus *Carnegiea gigantea* (Engelmann) Britton and Rose.[1c] By contrast, isoquinoline **2g** represents a synthetic precursor of necatorone,[25] a fungal pigment isolated from fruiting bodies of the basidiomycete *Lactarius plumbeus* (Bull.: Fr.) Gray [syn. *L. turpis* (Weinm.) Fr., *L. necator* (Bull.: Fr.) P. Karst. *ss. auct.*], which has been shown to possess strong mutagenic activity, as well as moderate antibiotic properties.[26]

Mechanistically, the Bischler–Napieralski reaction is well known to proceed through intramolecular electrophilic aromatic substitution of an iminoyl halide intermediate which is generated by the action of suitable phosphorus-based halogenating agents on a *N*-acyl β-arylethylamine. Once formed, the iminoyl halide species is trapped by an electron-rich aromatic ring such as an indole or a substituted phenyl ring.[6] In comparison to chlorine, bromine acts as a better leaving group and favors the formation of the intramolecularly tethered nitrilium ion, thus increasing the reaction rate and limiting the formation of undesirable side products, for example, elimination of byproducts such as nitriles and alkyl halides that may arise from von Braun degradation which is favored by higher temperatures.[6b] Such a mechanistic view is well corroborated by our own set of experimental data which reveal the superior performance of $TPPBr_2$ over $TPPCl_2$ in the cyclization of activated as well as inactivated β-phenylethylamides to 3,4-dihydroisoquinolines.

When compared to traditional Bischler–Napieralski-type cyclizations that have been used in the literature for the synthesis of 3,4-dihydroisoquinolines **2a**–**h** (Table 1, right-hand-side column), our $TPPBr_2$-mediated protocol features comparable to superior yields under much milder reaction conditions, even in the case of inactivated β-phenylethylamides **1a**,**b** which classically require treatment with harsh dehydrating agents upon prolonged heating at temperatures of 200 °C or above.

In conclusion, the peculiar halogenating potential of triphenyl phosphite–bromine[27] toward the activation of amides into the corresponding iminoyl bromides at temperatures as low as –60 °C has been conveniently employed in the framework of a Bischler–Napieralski-type cyclocondensation of *N*-acyl β-phenylethylamines to 3,4-dihydroisoquinolines under the mildest conditions ever reported in

Table 1 $TPPBr_2$-Promoted Bischler–Napieralski-Type Cyclization of *N*-Acyl-β-phenylethylamines to 3,4-Dihydroisoquinolines[a]

Entry	Substrate	R^1	R^2	R^3	R^4	Product	Yield (%)	Lit. yields (%)
1	**1a**	H	H	H	Me	**2a**	26 (0)[b]	23–53[9,28,29]
2	**1b**	H	OMe	H	Me	**2b**	27 (0)[b]	36[9,28,30]
3	**1c**	OMe	H	H	Me	**2c**	62	52–83[13,28,30]
4	**1d**	OCH_2O		H	Me	**2d**	90	79–86[31]
5	**1e**	OMe	OMe	H	Me	**2e**	80 (23)[b]	78–96[10a,13,16,17,31,32]
6	**1f**	OMe	OMe	H	Ph	**2f**	92	43–85[8a,10a,17,33]
7	**1g**	OMe	OMe	H	5-MeO-2-$O_2NC_6H_3$	**2g**	89	90–93[25b,34]
8	**1h**	OMe	OMe	OMe	Me	**2h**	73 (25)[b]	65[35]

[a] Reaction conditions: amide (1.0 mmol), $(PhO)_3P$ (1.2 mmol), Br_2 (1.2 mmol), Et_3N (1.3 mmol), CH_2Cl_2 (20 mL), –60 °C to r.t.
[b] Yields in parentheses refer to $TPPCl_2$-mediated reactions: –30 °C to r.t.

the literature. Yields range from good to excellent in the case of activated β-phenylethylamides and are comparable to or even higher than standard Bischler–Napieralski cyclizations. The extremely mild conditions employed make our $TPPBr_2$-based protocol most appealing as an alternative for the assembly of the 3,4-dihydroisoquinoline skeleton, especially in the presence of sensitive functional groups that might be prone to side reactions using classic methodologies.

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(23) (a) Acetamides **1a–e**,**h** were prepared by treatment of the parent β-phenylethylamine with Ac_2O, whereas for amides **1f**,**g** the appropriate acyl chloride was employed instead. Except for **1a** and **1b**, which were obtained from commercially available β-phenyl- and 4-methoxy-β-phenylethylamine, respectively, in all other cases the starting β-phenylethylamine was synthesized by condensation of the corresponding aromatic aldehyde with nitromethane in the presence of AcOH and NH_4OAc, and subsequent reduction of the resulting nitrostyrene with LAH in THF.[7f,23b] In particular, 3-methoxybenzaldehyde, piperonal, veratryl aldehyde, and 3,4,5-trimethoxybenzaldehyde were used for **1c**,**d**,**e–g**,**h**, respectively. In the latter case, the original procedure for the synthesis of mescaline was used.[23c] All synthesized β-phenylethylamines were used without any further purification. (b) Sawant, D.; Kumar, R.; Maulik, P. R.; Kundu, B. *Org. Lett.* **2006**, *8*, 1525. (c) Späth, E. *Monatsh. Chem.* **1919**, *40*, 129.

(24) **Synthesis of 6,7-Dimethoxy-1-phenyl-3,4-dihydroisoquinoline (2f)**
Triphenyl phosphite (0.89 mL, 3.41 mmol) was dissolved in anhyd CH_2Cl_2 (20 mL) and cooled to –60 °C. Bromine (0.18 mL, 3.41 mmol) and anhyd Et_3N (0.51 mL, 3.69 mmol) were introduced sequentially under argon flow. *N*-[2-(3,4-dimethoxyphenyl)ethyl]benzamide (**1f**, 819 mg, 2.84 mmol) was then added in one portion to the bright yellow solution maintained at the same temperature under vigorous stirring. The resulting mixture was gradually warmed to r.t. over a 2 h period, and left to stir overnight. Subsequently, the dark reaction mixture was extracted with 3 M HCl (3 × 15 mL), the combined aqueous layers were basified with 10% aq NaOH until pH = 11 and extracted with CH_2Cl_2 (3 × 15 mL).

The pooled organic phases were dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford the desired 3,4-dihydroisoquinoline **2f** as a brownish liquid (692 mg, 92% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.68 (2 H, t, *J* = 7.4 Hz, C*H*$_2$CH$_2$N), 3.67 (3 H, s, OMe), 3.77 (2 H, q, *J* = 7.4 Hz, CH$_2$C*H*$_2$N), 3.86 (3 H, m, OMe), 6.75 (2 H, s, arom.), 7.36–7.59 (5 H, m, Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.0, 47.6, 56.0, 56.1, 110.4, 111.7, 120.0, 121.5, 128.1, 128.7, 129.2, 129.8, 132.5, 139.1, 147.5. MS: *m/z* = 235 [M$^+$], 220, 204, 190, 177, 162,159, 146, 133, 110, 103, 91, 77, 65. Anal. Calcd for $C_{12}H_{13}ClN_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.59; H, 6.65; N, 5.08.

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