An Improved Synthesis of Various Racemic Polyphenolic Tetrahydroisoquinoline Alkaloids

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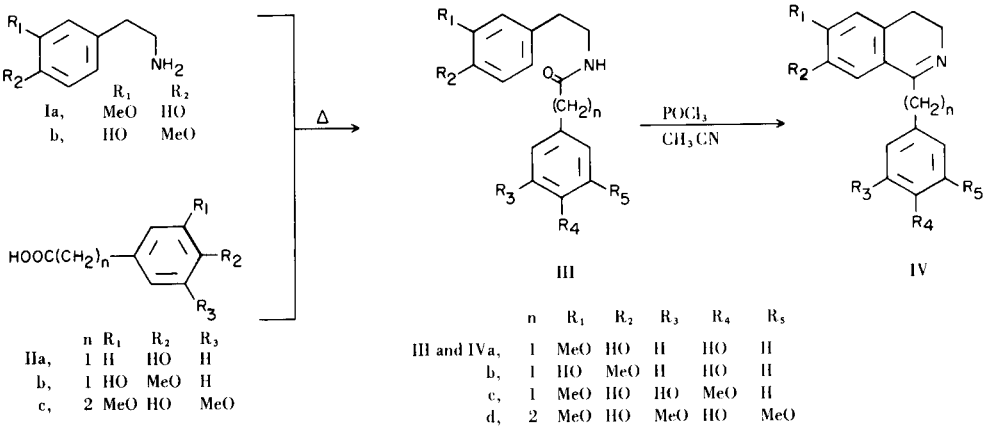
An improved and straightforward synthesis of (±)-coclaurine (Va), (±)-isococlaurine (Vb), (±)-reticuline (VIIIa) as well as an alternate route to an intermediate in the synthesis of (±)-multifloramine, the (±)-diphenol (VIIIb), is described.

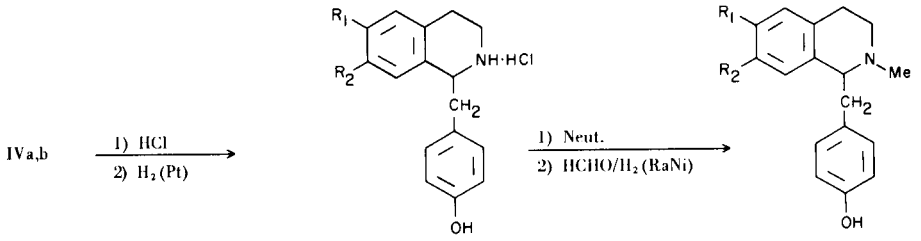
The synthesis of polyphenolic tetrahydroisoquinolines frequently involves the Bischler-Napieralski cyclization of appropriate benzyloxy-substituted phenethylaralkylamides. This procedure is rather lengthy since all of the ultimate phenolic functions are usually introduced as benzyl ethers which then must be removed at a subsequent stage. The benzyloxy-substituted phenethylamines required are customarily prepared from the corresponding β-nitrostyrene by reduction with the potentially hazardous lithium aluminum hydride. To circumvent these two major drawbacks, other routes have been attempted but the results have not been very encouraging. For example, Baxter and coworkers (1) reduced 4-benzyloxy-3-methoxyphenylacetonitrile with rhodium on alumina but obtained 2-(4-benzyloxy-3-methoxyphenyl)ethylamine in only 30% yield. Alternatively, Kratzl and Billek (2) condensed a hydroxy-substituted phenethylamine, prepared from the corresponding β-nitrostyrene by hydrogenation with an impractical excess of palladium on barium sulfate, with a phenylacetic acid to form a phenylacetamide containing a free phenolic function. However, prior to Bischler-Napieralski cyclization of this amide, the phenolic function was converted first to the corresponding benzyloxy derivative.

We recently reported (3) a direct synthesis of a monophenolic dihydroisoquinoline by cyclizing a monophenolic phenethylamide under standard Bischler-Napieralski conditions. This pathway avoided the tedious blocking and deblocking of the phenolic function as well as the use of lithium aluminum hydride since the requisite intermediate 2-(4-hydroxy-3-methoxyphenyl)ethylamine (Ia) could be obtained readily and practically by reduction of the corresponding β-nitrostyrene with palladium on carbon. The present report (4) describes straightforward syntheses of the alkaloids (±)-coclaurine (Va), (±)-isococlaurine (Vb) and (±)-reticuline (VIIIa), which heretofore have been prepared by the circuitous cyclization of protected diphenolic amides, as well as an alternate pathway for obtaining the (±)-diphenol VIIIb, the key intermediate for the synthesis of (±)-multifloramine.

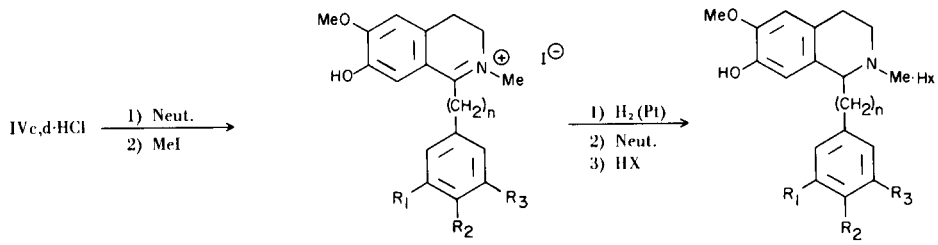
This new approach utilizing unprotected diphenolic amides is a considerable simplification over the standard method and is of preparative value. Yields of the racemic tetrahydroisoquinolines obtained by this route were consistently higher than those reported when protected diphenols were employed. In carrying out this modification, acetonitrile (5) proved to be superior to chloroform as a solvent in effecting cyclodehydration with phosphorus oxychloride. Thus, (±)-coclaurine (Va) was obtained in 61% overall yield from the easily accessible (3) 2-(4-hydroxy-3-methoxyphenyl)ethylamine (Ia) in the following way. Condensation of Ia with 4-hydroxyphenylacetic acid (IIa) afforded the diphenolic amide (IIIa) which was directly cyclized to the diphenolic 3,4-dihydroisoquinoline (IVa) with phosphorus oxychloride in acetonitrile. Catalytic reduction of IVa as its hydrochloride gave the known (2) alkaloid (Va) which was further converted to the known (6) *N*-methyl derivative (VIa). Similarly, the isomeric alkaloid, (±)-isococlaurine (Vb), was prepared in 57% yield from 2-(3-hydroxy-4-methoxyphenyl)ethylamine (Ib). For this purpose, Ib was more conveniently obtained from 3-hydroxy-4-methoxy-β-nitrostyrene by hydrogenation over palladium on carbon in dilute hydrochloric acid rather than by the customary cumbersome reduction with lithium aluminum hydride (7). Cyclization of the diphenolic amide (IIIb), prepared from Ib and the hydroxy acid (IIa), with phosphorus oxychloride in acetonitrile afforded the diphenolic 3,4-dihydroisoquinoline (IVb) which was transformed, without further purification, *via* catalytic reduction to the known (9,10)



	n	R_1	R_2	R_3	R_4	R_5
IIa,	1	H	HO	H		
b,	1	HO	MeO	H		
c,	2	MeO	HO	MeO		
III and IVa,	1	MeO	HO	H	HO	H
b,	1	HO	MeO	H	HO	H
c,	1	MeO	HO	HO	MeO	H
d,	2	MeO	HO	MeO	HO	MeO



	R_1	R_2
V and VIa,	MeO	HO
b,	HO	MeO



	n	R_1	R_2	R_3
VII and VIIIa,	1	HO	MeO	H
b,	2	MeO	HO	MeO

alkaloid (Vb). The latter was further transformed into the known (9,10) *N*-methylisococlaurine (VIb).

Having thus established that simple diphenolic amides can be efficiently cyclized to give directly 6- and 7-hydroxy-1-(4-hydroxybenzyl)-3,4-dihydroisoquinolines, it was of interest to demonstrate the applicability of the method to even more highly hydroxylated derivatives. For this purpose the hydroxyphenethylamine (Ia) was condensed with the hydroxy-methoxyphenylacetic acid (IIIb) (11) and the hydroxy-dimethoxyphenylpropionic acid (IIc) (12) to form the diphenolic amides, IIIc and IIId, respectively. Cyclization of IIIc and IIId under Bischler-Napieralski conditions afforded the corresponding diphenolic 3,4-dihydroisoquinolines, isolated as the crystalline hydrochlorides, IVc and IVd. The latter compound, IVd, obtained in 67% overall yield from Ia, was identical with a sample of IVd previously prepared by another route (3). This newest mode of preparing IVd is therefore an alternate and facile route to the synthesis of VIIIb, a key intermediate in the synthesis of (±)-multifloramine.

Neutralization of the diphenolic dihydroisoquinoline (IVc) followed by quaternization with methyl iodide gave VIIa which was hydrogenated over platinum to afford directly the known (1,13) alkaloid (±)-reticuline perchlorate (VIIIa) in a 33% overall yield from the hydroxyphenethylamine (Ia). The value of utilizing unprotected phenolic amides in the Bischler-Napieralski cyclization as the preferred synthetic pathway to certain polyphenolic racemic tetrahydroisoquinolines is thus demonstrated.

EXPERIMENTAL (14)

N-(4-Hydroxy-3-methoxyphenethyl)-(4-hydroxyphenyl)acetamide (IIIa).

A mixture of 4.4 g. (26.3 mmoles) of 2-(4-hydroxy-3-methoxyphenyl)ethylamine (Ia) (3) and 4.0 g. (26.3 mmoles) of 4-hydroxyphenylacetic acid (IIa) was heated in a nitrogen atmosphere at 190° for 2 hours. The reaction product was cooled, dissolved in ethyl acetate and the solution washed with 1*N* hydrochloric acid and then with 5% sodium bicarbonate and evaporated. The residue was crystallized from a mixture of ethyl acetate and ether to give 7.2 g. (91%) of IIIa, m.p. 132-134°. A specimen was prepared from a mixture of ethyl acetate and ether, m.p. 133-134°; ν max (potassium bromide): 3410 (NH), 3240 (OH), 2700-2500 (associated OH), 1650 (amide I), 1550 cm^{-1} (amide II).

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36. Found: C, 67.72; H, 6.58.

7-Hydroxy-6-methoxy-1-(4-hydroxybenzyl)-3,4-dihydroisoquinoline (IVa).

To a stirred and refluxing solution of 5 g. (17 mmoles) of IIIa in 100 ml. of acetonitrile was added 16.8 g. (110 mmoles) of phosphorus oxychloride over 15 minutes. The reaction mixture was refluxed for 1 hour, cooled and evaporated under reduced pressure. The residual gum was dissolved in a minimum of acetonitrile, diluted with ethyl acetate and the resulting turbid mixture was washed with saturated sodium bicarbonate and evaporated to give 4.9 g. (100%) of IVa as a yellow gum which could be used in the next step without further purification. For characterization, an aliquot of IVa was converted to the picrate, m.p. 143-145° (from ethanol-water) [(2): m.p. 200-201°]; λ max (ethanol), 225 (infl) (ϵ, 29,700), 310 (sh) (ϵ, 11,400), 358 mμ (ϵ, 19,900); nmr, δ 3.08, 3.85 (2 CH_2), 3.93 (OCH_3), 4.28 (CH_2), 6.77, 7.17 (di-substituted benzene), 7.11, 7.45 (2 aromatics), 8.53 (2 aromatics of picric acid), 1250 (NH^+).

Anal. Calcd. for $C_{23}H_{20}N_4O_{10}$: C, 53.91; H, 3.93. Found: C, 53.96; H, 4.05.

(±)-Coclaurine Hydrochloride Monohydrate (Va).

A solution of 1.98 g. (6.65 mmoles) of IVa in ethanol was rendered acidic with ethanolic hydrogen chloride and evaporated. The residue was dissolved in 200 ml. of ethanol and hydrogenated in the presence of 0.5 g. of platinum oxide at 3 atmospheres and room temperature until the hydrogen uptake had ceased. The catalyst was filtered, the filtrate evaporated and the residue crystallized from water to give 1.5 g. (67% based on IIIa) of Va, m.p. 261-263° [(2): m.p. 255-256°]; λ max (ethanol), 226 (ϵ, 16,100), 284 mμ (ϵ, 5,450); nmr, δ 2.80-3.50 (3 CH_2), 3.76 (OCH_3), 4.40 (methine), 6.50-7.20 (6 aromatics), 9.0 and 9.5 (2 OH, NH^+).

Anal. Calcd. for $C_{17}H_{19}NO_3 \cdot HCl \cdot H_2O$: C, 60.09; H, 6.53. Found: C, 60.39; H, 6.59.

(±)-*N*-Methylcoclaurine (VIa).

A solution of 680 mg. (2 mmoles) of Va in 75 ml. of methanol was neutralized with a methanolic solution of sodium methylate, 0.3 ml. of 37% formaldehyde was added and the mixture hydrogenated in the presence of 3 g. of Raney nickel at 3 atmospheres at room temperature until the hydrogen uptake had ceased. The mixture was filtered, the filtrate evaporated and the residue crystallized from a mixture of benzene and petroleum ether to give 390 mg. (65%) of VIa, m.p. 163-165° [(6): m.p. 161-162°]; ν max (potassium bromide) 3350 (OH), 2700-2500 (associated OH), 1615, 1600, 1520 (aromatic), 1260 cm^{-1} (OCH_3 and OH).

Anal. Calcd. for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07. Found: C, 72.15; H, 6.99.

2-(3-Hydroxy-4-methoxyphenyl)ethylamine Hydrochloride (Ib·HCl).

A mixture of 39.2 g. (0.2 mole) of 3-hydroxy-4-methoxy-β-nitrostyrene (7) and 40 ml. of concentrated hydrochloric acid was diluted with water to 900 ml. and hydrogenated in the presence of 18 g. of 10% palladium on carbon at 33 atmospheres at 80° until the hydrogen uptake had ceased. The catalyst was filtered, the colorless filtrate evaporated and the residue crystallized from a mixture of ethanol and ether to give 32.6 g. (79%) of Ib·HCl, m.p. 204-206° [(7): m.p. 206-207°].

N-(3-Hydroxy-4-methoxyphenethyl)-(4-hydroxyphenyl)acetamide (IIIb).

An aqueous solution of 3.04 g. (15 mmoles) of Ib·HCl was rendered alkaline with ammonium hydroxide and extracted with methylene chloride. The organic extract was evaporated and the residue reacted with 2.28 g. (15 mmoles) of 4-hydroxyphenyl acetic acid (IIa) according to the procedure given for the preparation of IIIa to afford 4.38 g. (97%) of IIIb, m.p. 187-189°. An analytical specimen was prepared from methanol, m.p. 189-191°; ν max (potassium bromide): 3350 (NH and OH), 2700-2500 (associated OH), 1650 (amide I), 1525 cm^{-1} (amide II).

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36. Found: C, 67.79; H, 6.58.

6-Hydroxy-7-methoxy-1-(4-hydroxybenzyl)-3,4-dihydroisoquinoline (IVb).

Reaction of 4.0 g. (13.6 mmoles) of IIIb with 13.4 g. (89 mmoles) of phosphorus oxychloride in 80 ml. of acetonitrile according to the procedure given for the preparation of IVa afforded 2.6 g. (67%) of IVb as a yellow gum which could be used in the next step without further purification. For characterization, an aliquot of IVb was converted to the picrate, m.p. 164-166° (from ethanol); λ max (ethanol), 220 (infl) (ε, 29,900), 310 (sh) (ε, 10,500), 358 mμ (ε, 18,400); nmr, δ 3.06, 3.85 (2 CH_2), 3.92 (OCH_3), 4.27 (CH_2), 6.77, 7.17 (di-substituted benzene), 7.11, 7.43 (2 aromatics), 8.57 (2 aromatics of picric acid), 9.50 (OH), 12.50 (NH^+).

Anal. Calcd. for $C_{23}H_{20}N_4O_{10}$: C, 53.91; H, 3.93. Found: C, 53.71; H, 3.81.

(±)-Isococlaurine Hydrochloride Hemihydrate (Vb).

Conversion of 1.3 g. (4.36 mmoles) of IVb to its hydrochloride followed by reduction according to the procedure given for the preparation of Va afforded, after crystallization from a mixture of acetone and ether, 1.3 g. (59% based on IIIb) of Vb, m.p. 178-180° [(8) m.p. 215° for anhydrous salt; (9): m.p. 156-157° for monohydrate]; λ max (ethanol): 226 (ε, 13,500), 284 mμ (ε, 4,500); nmr, δ 2.70-2.40 (3 CH_2), 4.40 (methine), 4.53 (OCH_3), 6.35-7.30 (6 aromatics), 9.75 (2 OH, NH^+).

Anal. Calcd. for $C_{17}H_{19}NO_3 \cdot HCl \cdot \frac{1}{2}H_2O$: C, 61.72; H, 6.40. Found: C, 61.77, 61.44; H, 6.55, 6.38.

(±)-*N*-Methylisococlaurine (VIb).

A mixture of 500 mg. (1.5 mmoles) of Vb and 0.2 ml. of 37% formaldehyde was reduced with 3 g. of Raney nickel according to the procedure given for VIa to afford, after crystallization from acetone, 260 mg. (58%) of VIb, m.p. 228-230° [(9): m.p. 225-226°; (10) m.p. 218-219°]; ν max (potassium bromide), 3420 (OH), 2700-2500 (associated OH), 1613, 1592, 1520 (aromatic), 1275 and 1260 cm^{-1} (OCH_3 and OH).

Anal. Calcd. for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07. Found: C, 72.07; H, 7.27.

N-(4-Hydroxy-3-methoxyphenethyl)-(3-hydroxy-4-methoxyphenyl)acetamide (IIIc).

A mixture of 12.4 g. (74 mmoles) of Ia (3) and 13.5 g. (74 mmoles) of 3-hydroxy-4-methoxyphenylacetic acid (IIb) (11) was reacted according to the procedure given for the preparation of IIIa to afford, after crystallization from a mixture of ethyl acetate and ether, 19.1 g. (78%) of IIIc, m.p. 124-126°; ν max (chloroform), 3540 (OH), 3420 (NH), 1655 (amide I), 1520 cm^{-1} (amide II).

Anal. Calcd. for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39. Found: C, 65.25; H, 6.53.

7-Hydroxy-6-methoxy-1-(3-hydroxy-4-methoxybenzyl)-3,4-dihydroisoquinoline Hydrochloride (IVc·HCl).

Reaction of 4.5 g. (13.6 mmoles) of IIIc with 13.4 g. (89 mmoles) of phosphorus oxychloride in 80 ml. of acetonitrile according to the procedure given for the preparation of IVa gave a yellow oil which was dissolved in ethanol, rendered acidic with ethanolic hydrogen chloride and evaporated. The residue was crystallized from a mixture of ethanol, acetone and ether to afford 2.9 g. (61%) of IVc·HCl as pale yellow platelets, m.p. 218-220°. An analytical specimen was prepared from a mixture of methanol, acetone and ether, m.p. 219-221°; λ max (methanol), 233 (ε, 14,900), 244 (ε, 14,500), 304 (ε, 8,820), 362 mμ (ε, 7,000); λ max (0.1 *N* hydrochloric acid), 241 (ε, 16,020), 301 (ε, 9,420), 352 mμ (ε, 8,700); λ max (0.1 *N* potassium hydroxide), 241 (ε, 28,800), 287 (ε, 6,780), 340 mμ (ε, 4,880); nmr, δ 3.00, 3.85, 4.33 (3 CH_2), 3.72, 3.90 (2 OCH_3), 6.84 (3 aromatics), 7.08, 7.52 (2 aromatics), 8.30-10.30 (2 OH, NH^+).

Anal. Calcd. for $C_{18}H_{19}NO_4 \cdot HCl$: C, 61.80; H, 5.76; N, 4.01. Found: C, 61.47; H, 5.95; N, 4.03.

7-Hydroxy-6-methoxy-2-methyl-1-(3-hydroxy-4-methoxybenzyl)-3,4-dihydroisoquinolinium Iodide (VIIa).

To a methanolic solution of 2.62 g. (7.5 mmoles) of IVc·HCl was added a methanolic solution of 0.4 g. (7.5 mmoles) of sodium methylate. The mixture was evaporated and the residue extracted with three 20 ml. portions of methylene chloride. The extracts were evaporated, the residue was dissolved in 25 ml. of methanol, 3 ml. of methyl iodide was added and the solution was stored at room temperature overnight and then evaporated. The residue was crystallized from a mixture of methanol and ether to give 2.8 g. (83%) of VIIa as yellow prisms, m.p. 195-198°. An analytical specimen was prepared from a mixture of methanol and ether, m.p. 198-200°; λ max (methanol): 248 (ε, 17,600), 309 (ε, 10,800), 367 mμ (ε, 9,850); λ max (0.1 *N* hydrochloric acid), 221 (ε, 26,200), 244 (sh) (ε, 16,960), 305 (ε, 9,800), 359 mμ (ε, 9,650); λ max (0.1 *N* potassium hydroxide), 267 (ε, 22,200), 319 (ε, 10,150), 420 mμ (ε, 5,760); nmr, δ 3.14, 4.12, 4.45 (3 CH_2), 3.35 (NCH_3), 3.78, 3.98 (2 OCH_3), 6.70 (2 aromatics), 6.90, 7.17, 7.43 (3 aromatics), 9.06, 9.58 (2 OH).

Anal. Calcd. for $C_{19}H_{22}INO_4$: C, 50.12; H, 4.87; N, 3.08. Found: C, 50.22; H, 4.79; N, 3.47.

(±)-Reticuline Perchlorate (VIIIa).

A solution of 2.2 g. (4.65 mmoles) of VIIa in 200 ml. of methanol was hydrogenated in the presence of 0.2 g. of platinum oxide at 3 atmospheres and room temperature until the hydrogen uptake had ceased. The catalyst was filtered, the filtrate evaporated and the residue distributed between a mixture of ethyl acetate and saturated sodium bicarbonate solution. The organic extract was separated and evaporated. The residue was dissolved in ethanol, rendered acidic with 70% perchloric acid and an excess of ether added to precipitate a gum. The supernatant liquid was decanted and the gum crystallized from a mixture of ethanol and ether to give 1.75 g. (84%) of VIIIa as colorless prisms, m.p. 125-128°. An analytical specimen was prepared from ethanol, m.p. 128-130° [(1) m.p. 108° for hemihydrate; (13) m.p. 144-145° with sintering at 100° for dihydrate]; λ max (methanol), 225 (sh) (ε, 13,300), 284 mμ (ε, 7,100); nmr, δ 2.70-3.90 (3 CH_2), 3.30 (NCH_3), 3.78 (2 OCH_3), 4.52 (methine), 6.20 (1 aromatic), 6.80-7.10 (4 aromatics), 8.85 (2 OH).

Anal. Calcd. for $C_{19}H_{23}NO_4 \cdot HClO_4$: C, 53.09; H, 5.63; N, 3.26. Found: C, 52.96; H, 5.79; N, 3.26.

N-(4-Hydroxy-3-methoxyphenethyl)-3-(3,5-dimethoxy-4-hydroxyphenyl)propionamide (IIId).

A mixture of 5 g. (30 mmoles) of Ia and 6.8 g. (30 mmoles) of 3,5-dimethoxy-4-hydroxypropionic acid (IIc) (12) was reacted according to the procedure given for IIIa to afford, after crystallization from ether, 8.9 g. (79%) of IIId, m.p. 100-102°; ν max (chloroform), 3570 (OH), 3450 (NH), 1660 (amide I), 1520

cm^{-1} (amide II).

Anal. Calcd. for $C_{20}H_{25}NO_6$: C, 63.98; H, 6.71. Found: C, 63.78; H, 6.74.

7-Hydroxy-6-methoxy-1-(3,5-dimethoxy-4-hydroxyphenethyl)-3,4-dihydroisoquinoline Hydrochloride (IVd·HCl).

Reaction of 7.5 g. (20 mmoles) of IIId and 25.2 g. (165 mmoles) of phosphorus oxychloride according to the procedure given for IVc afforded, after crystallization from a mixture of ethanol and ether, 6.7 g. (85%) of IVd·HCl, m.p. 213-215°, identical by m.m.p., tlc, and nmr to an authentic sample (3) of IVd·HCl.

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(5) We are grateful to our colleague Dr. F. Schenker of these laboratories for suggesting acetonitrile as a solvent superior to chloroform in Bischler-Napieralski cyclizations.

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