

A Significantly Improved Condition for Cyclization of Phenethylcarbamates to N-Alkylated 3,4-Dihydroisoquinolones

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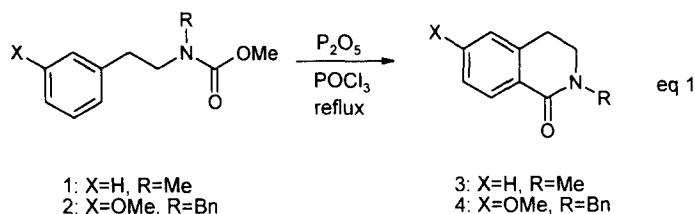
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Abstract: Secondary phenethylcarbamates undergo a Bischler-Napieralski cyclization promoted by phosphorus pentoxide in refluxing phosphorus oxychloride to afford N-alkylated 3,4-dihydroisoquinolones in high yields.
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The Bischler-Napieralski reaction of phenethylamides and carbamates has been a powerful method for synthesis of 3,4-dihydroisoquinolines and related heterocyclic compounds including 3,4-dihydroisoquinolones.¹ Previous reports on synthesis of 3,4-dihydroisoquinolones by this reaction involve the ring closure of isocyanates with POCl₃,² SnCl₄,³ BF₃ etherate,⁴ and a mixture of SnCl₄ and POCl₃,⁵ as well as cyclization of carbamates with PPA,⁶ POCl₃,⁷ and Tf₂O.⁸ These conditions usually require an electron-donating group such as the alkoxy group on the aromatic ring, and substrates lacking electron-donating groups often failed to cyclize or gave low yields. As we required an efficient procedure for cyclization of secondary phenethylcarbamates, we describe here our finding that P₂O₅ in refluxing POCl₃ efficiently promotes cyclization of phenethylcarbamates⁹ to 3,4-dihydroisoquinolones in very high yields.

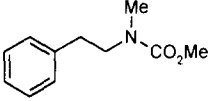
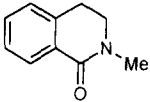
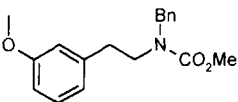
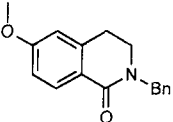
We employed non-substituted carbamate **1** lacking the electron-donating group for our initial study. Most of the reported conditions such as POCl₃, POCl₃ in CH₃CN, PPA, Tf₂O and SnCl₄ failed to effect the cyclization to isoquinolone **3**. Carbamate **2** bearing a *meta*-methoxy group underwent cyclization to **4** in low to moderate yield. In contrast, the combination of P₂O₅ and POCl₃ induced smooth cyclization of both carbamates **1** and **2**, yielding quantitatively the isoquinolones **3**¹⁰ and **4**. From carbamate **2**, an 8:1 mixture of



para- and *ortho*-products was obtained. **Table 1** outlines a series of experiments in which the P₂O₅/POCl₃ system is compared with the other reported conditions. A combination of P₂O₅/POCl₃ may be a stronger dehydration medium, one can suppose it would enhance formation of an intermediary iminium ion, which could then react fast with the aromatic ring.¹¹

As shown in **Table 2**, 4-methoxy- and 4-methylphenethylcarbamates (**Entries 3 and 5**) show the same excellent result, as those halo-substituted carbamates, regardless of the position of the substituent

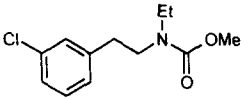
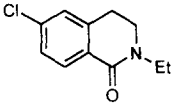
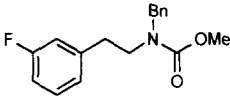
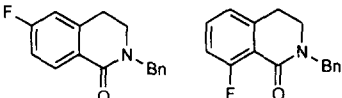
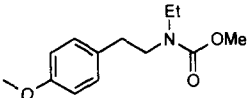
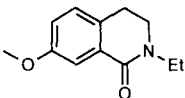
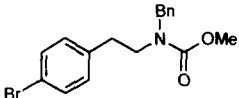
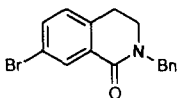
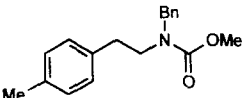
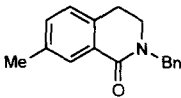
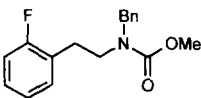
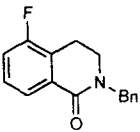
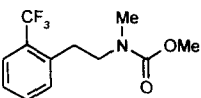
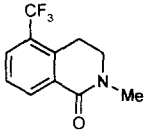
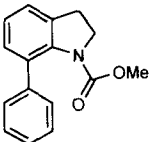
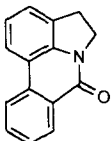
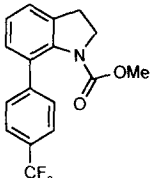
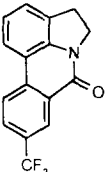
Table 1

Substrate	Product	Condition	Time(h)	Temp.(°C)	Yield(%)
 1	 3	POCl ₃	24	100	5
		POCl ₃ /CH ₃ CN	24	81	N.R.
		PPA	24	100	19
		SnCl ₄ /POCl ₃	12	r.t.	N.R.
		Tf ₂ O/DMAP	12	r.t.	N.R.
		P₂O₅/POCl₃	2	100	98
 2	 4	POCl ₃	24	100	39
		POCl ₃ /CH ₃ CN	24	81	5
		PPA	24	100	45
		SnCl ₄ /POCl ₃	12	r.t.	37
		P₂O₅/POCl₃	2	100	96

(**Entries 1 and 2** with **4 and 6**). 4-Bromo-phenethylcarbamate gave a somewhat lower yield (67%, **Entry 4**). 3-Chloro and 3-fluorophenethylcarbamates (**Entries 1 and 2**) gave a mixture of *para*- and *ortho*-products predominating the *para*-isomer. With electron-withdrawing CF₃ substituted carbamates (**Entries 7 and 9**), the reaction time and yield showed no significant difference.¹²

The following procedure is representative: To a solution of N-benzyl-N-(methoxy)carbonyl-3-methoxyphenethylamine (2.0 g, 6.70 mmol) in POCl₃ (10 mL) was added P₂O₅ (2.0 g, 13.5 mmol). The resulting mixture was refluxed for 2 hours. POCl₃ was then evaporated and the residue was quenched with ice-water. The mixture was neutralized with Na₂CO₃, extracted with ethyl acetate and the extract was dried over MgSO₄ and filtered. The filtrate was concentrated and the residue was chromatographed on silica gel (hexane/ether, 3:1) to give N-benzyl-6-methoxy-3,4-dihydroisoquinolone as a white solid (1.50 g, 86%). mp: 103-105°C. ¹H NMR (CDCl₃, 400MHz): 8.14 (d, J=8.5 Hz, 1H, H-8), 7.38-7.30 (m, 5H, PhH), 6.90 (dd, J=8.5, 2.5 Hz, 1H, H-7), 6.69 (d, J=2.5Hz, 1H, H-5), 4.82 (s, 2H, PhCH₂), 3.88 (s, 3H, OCH₃), 3.51 (t, J=6.5 Hz, 2H, NCH₂), 2.94 (t, J=6.5 Hz, 2H, ArCH₂). MS *m/e* 268 (100, MH⁺). Anal. Calcd for C₁₇H₁₇NO₂: C, 76.37; H, 6.41; N, 5.04. Found: C, 76.17; H, 6.42; N, 5.04. Continued elution afforded N-benzyl-8-methoxy-3,4-dihydro-isoquinolone as a white solid (0.21 g, 11%). mp: 81-83°C. ¹H NMR (CDCl₃, 400MHz): 7.41-7.28 (m, 6H, PhH and H-6), 6.94 (d, J=8.5 Hz, 1H, H-7), 6.77 (d, J=7.5Hz, 1H, H-5), 4.81 (s, 2H, PhCH₂), 3.99 (s,

Table 2: Cyclization of Secondary Phenethylcarbamates with P₂O₅/POCl₃

Entry	Substrates	Products ^a	Time(h)	Yield(%) ^b
1		 6:1 ^c	2	94 ^d
2		 11:1 ^c	4	90 ^d
3 ^e			2	98
4			2	67
5 ^e			2	94
6 ^e			4	91
7 ^e			4	95
8 ^e			3	95 ¹³
9 ^e			4	90

a) All products have satisfied ¹H NMR, ¹³C NMR, MS and high resolution MS or elemental analysis. b) isolated yield by column chromatograph. c) ratio determined by proton NMR of crude mixture and both isomers were isolated by column chromatography. d) combined yield of two isomers. e) satisfied NMR and MS for crude products.

3H, OCH₃), 3.46 (t, J=6.5 Hz, 2H, NCH₂), 2.85 (t, J=6.5 Hz, 2H, ArCH₂). MS *m/e* 268 (100, MH⁺). Anal. Calcd for C₁₇H₁₇NO₂: C, 76.37; H, 6.41; N, 5.04. Found: C, 76.42; H, 6.45; N, 4.96.

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