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LETTERS

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

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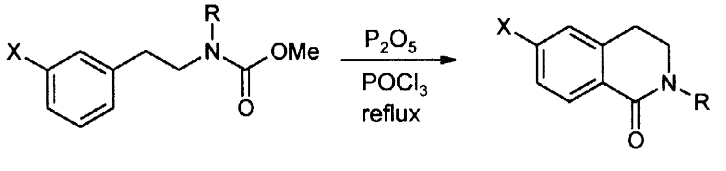
Abstract: Secondary phenethylcarbamates undergo a Bischler-Napieralski cyclization promoted by phosphorus pentoxide in refluxing phosphorus oxychloride to afford N-alkylated 3,4-dihydroisoquinolones in high yields.

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 $POCl_3$,[2] $SnCl_4$,[3] BF_3 etherate,[4] and a mixture of $SnCl_4$ and $POCl_3$,[5] as well as cyclization of carbamates with PPA,[6] $POCl_3$,[7] and Tf_2O.[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 P_2O_5 in refluxing $POCl_3$ efficiently promotes cyclization of phenethylcarbamates[9] 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 $POCl_3$, $POCl_3$ in CH_3CN, PPA, Tf_2O and $SnCl_4$ 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 P_2O_5 and $POCl_3$ induced smooth cyclization of both carbamates **1** and **2**, yielding quantatively 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 $P_2O_5/POCl_3$ system is compared with the other reported conditions. A combination of $P_2O_5/POCl_3$ 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]



eq 1

1: X=H, R=Me
2: X=OMe, R=Bn

3: X=H, R=Me
4: X=OMe, R=Bn

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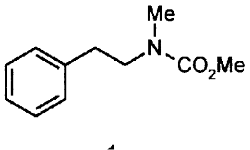
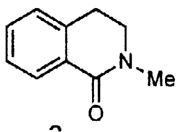
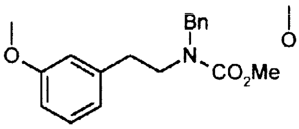
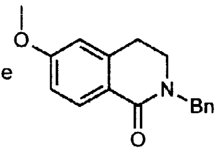
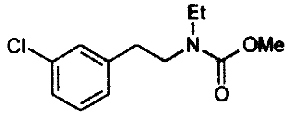
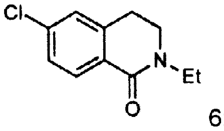
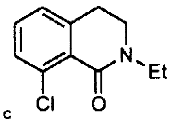
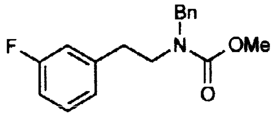
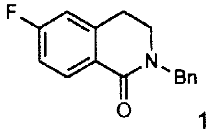
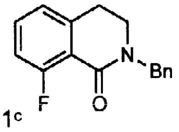
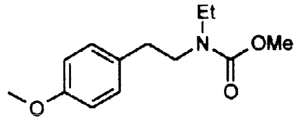
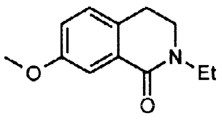
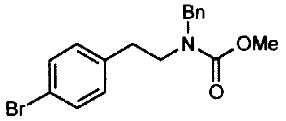
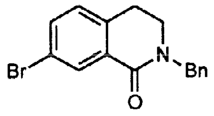
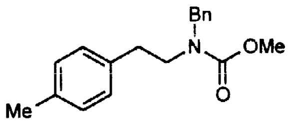
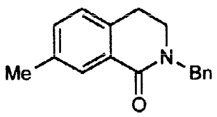
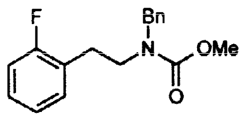
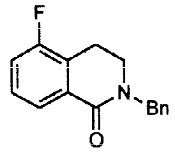
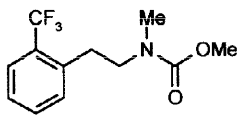
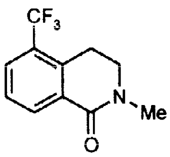
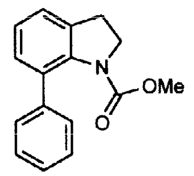
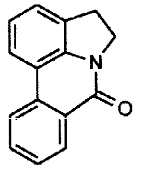
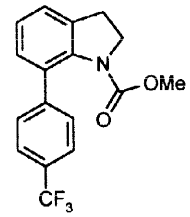
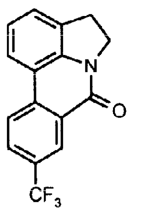
As shown in **Table 2**, 4-methoxy- and 4-methylphenethylcarbamates (**Entries** 3 and 5) show the same excellent result, as those halo-substituted carbamates, regardless of the position of the substituent (**Entries 1** and **2** with **4** and **6**). 4-Bromo- phenethylcarbamate gave a somewhat lower 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 CF_3 substituted carbamates (**Entries 7 and 9**), the reaction time and yield showed no significant difference.[12]

Table 1

Substrate	Product	Condition	Time(h)	Temp.(°C)	Yield(%)
 1	 3	$POCl_3$	24	100	5
		$POCl_3$/ CH_3CN	24	81	N.R.
		PPA	24	100	19
		$SnCl_4$/ $POCl_3$	12	r.t.	N.R.
		Tf_2O/ DMAP	12	r.t.	N.R.
		P_2O_5/ $POCl_3$	**2**	**100**	**98**
 2	 4	$POCl_3$	24	100	39
		$POCl_3$/ CH_3CN	24	81	5
		PPA	24	100	45
		$SnCl_4$/ $POCl_3$	12	r.t.	37
		P_2O_5/ $POCl_3$	**2**	**100**	**96**

The following procedure is representative: To a solution of N-benzyl-N-(methoxy)carbonyl-3-methoxyphenethylamine (2.0 g, 6.70 mmol) in $POCl_3$ (10 mL) was added P_2O_5 (2.0 g, 13.5 mmol). The resulting mixture was refluxed for 2 hours, $POCl_3$ was then evaporated and the residue was quenched with ice-water. The mixture was neutralized with Na_2CO_3, extracted with ethyl acetate and the extract was dried over $MgSO_4$ 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. ^{1}H NMR ($CDCl_3$, 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, $PhCH_2$), 3.88 (s, 3H, OCH_3), 3.51 (t, J=6.5 Hz, 2H, NCH_2), 2.94 (t, J=6.5 Hz, 2H, $ArCH_2$). MS *m/e* 268 (100, MH$^+$). Anal. Calcd for $C_{17}H_{17}NO_2$: 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. ^{1}H NMR ($CDCl_3$, 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, $PhCH_2$), 3.99 (s,

Table 2: Cyclization of Secondary Phenethylcarbamates with $P_2O_5/POCl_3$

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 ^{1}H NMR, ^{13}C NMR, MS and high resolution MS or elemnetal 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, OCH_3), 3.46 (t, J=6.5 Hz, 2H, NCH_2), 2.85 (t, J=6.5 Hz, 2H, $ArCH_2$). MS *m/e* 268 (100, MH^+). Anal. Calcd for $C_{17}H_{17}NO_2$: C,76.37; H, 6.41; N,5.04. Found: C,76.42; H, 6.45; N, 4.96.

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References and notes.

1 Fodor, G.; Nagubandi, S. *Tetrahedron* **1980**, *36*, 1279-1300.

2. Banwell, M. G.; Cowden, C. J.; Mackay, M. F. *J. Chem. Soc., Chem. Commun.* **1994**, 61-62. (b) Angle, S. R.; Boyce, J. P. *Tetrahedron Lett.* **1995**, *36*, 6185-6188. (c) Banwell, M. G.; Wu, A. W. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2671-2672.

3. Tsuda, Y.; Isobe, K.; Toda, J. *Heterocycles* **1976**, *5*, 157-159.

4. (a) Ohta, S.; Kimoto, S. *Chem. Pharm. Bull.* **1976**, *24*, 2969-2976. (b) Balazs, L.; Nyerges, M.; Kadas, I.; Toke, L. *Synthesis* **1995**, 1373-1375. (c) *Synthesis* **1994**, 73-76.

5. Tanaka, H.; Nagai, Y.; Irie, H.; Uyeo, S.; Kuno, A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 873-878.

6. (a) Smith, P. A. S.; Kan, R. O. *J. Am. Chem. Soc.* **1960**, *82*, 4753-4754. (b) Hendrickson, J. B.; Bogard, T. L.; Fisch, M. E.; Grossert, S.; Yoshimura, N. *J. A m. Chem. Soc.* **1974**, *96*, 7781-7789. (c) Umezawa, B.; Hoshino, O.; Sawaki, H.; Mori, K. *Chem. Pharm. Bull.* **1980**, *28*, 1003-1005.

7. Martin, S. F.; Tu, C.-j. *J. Org. Chem.* **1981**, *46*, 3764-3765.

8. 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**, 2551-2553.

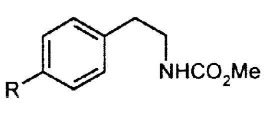
9. All phenethylcarbamates were made from their corresponding amines by well precedented procedures and carbamates from **Entries 8** and **9** were synthesized according to Banwell's procedure.[8]

10. Gramain, J. C., Simonet, N., Vermeersch, G., Febray-Garot, N., Caplain, S., Lablache-Combier, A. *Tetrahedron* **1982**, *38*, 539-550.

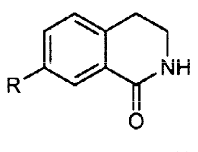
11. Fodor, G., Gal, J., Phillips, B. A. *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 919-920.

12. Hutchings, R. H., Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 1004-1013.

13. A preliminary study showed that $P_2O_5/POCl_3$ promoted cyclization of primary phenethylcarbamates **5a** and **5b** to give 3,4-dihydroisoquinolones **6a** and **6b** in low yields.



5a: R=H
5b: R=OMe



6a: R=H 36%
6b: R=OMe 25%