A Practical Synthesis of Cabergoline

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · NOVEMBER 2002

Impact Factor: 4.72 · DOI: 10.1021/jo0203847 · Source: PubMed

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A Practical Synthesis of Cabergoline

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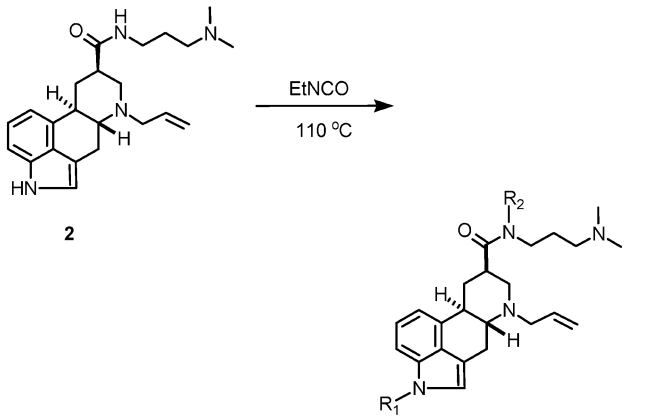
Received June 5, 2002

Abstract: Cabergoline is an *N*-acylurea derived from 9,10-dihydrolysergic acid, which is a potent prolactin inhibitor. It is marketed by Pharmacia as Dostinex for the treatment of hyperprolactinemia and is currently under active development for the treatment of a variety of CNS disorders. In the existing process, the *N*-acylurea is formed by the reaction of an amide with a large excess of ethyl isocyanate at elevated temperatures. An improved process was developed that eliminates this hazardous reaction. The amide is reacted with phenyl chloroformate and then with ethylamine, which provides a mild and efficient means of forming the unsymmetrical *N*-acylurea.

Natural ergot alkaloids and various synthetic derivatives exhibit a wide range of biological activity, and a number of them have potent dopamine agonist properties with applications as anti-Parkinson drugs and as prolactin inhibitors. Cabergoline was prepared as part of a program at Pharmacia to examine a series of amides derived from 9,10-dihydrolysergic acid and was found to be a potent long-lasting prolactin inhibitor.[1] It is currently marketed by Pharmacia as Dostinex for the treatment of hyperprolactinemia and is also being investigated for the management of Parkinson's disease and a number of other CNS disorders.

Cabergoline contains an unusual *N*-acylurea functionality appended to the C-8 carboxylic acid of *N*-allyldihydrolysergic acid (cabergolinic acid). In the current synthetic process, this group is introduced by the reaction of the amide **2** with ethyl isocyanate (Scheme 1). Although this process provides a direct method for the preparation of cabergoline, it has a number of drawbacks, the most serious of which is the use of hazardous ethyl isocyanate at elevated temperatures. Since this reaction is an equilibrium, it requires the use of a large excess of ethyl isocyanate (up to 40 equiv) for reasonable conversion and must be conducted at 100 °C in toluene, 40 °C above the boiling point of ethyl isocyanate. The use of large quantities of toxic ethyl isocyanate under drastic reaction conditions presents a serious safety hazard for the large-scale preparation of cabergoline. In addition to the safety-related issues, conversion to **1** is incomplete and competitive acylation of the indole nitrogen to give compounds **3** and **4** is a serious side reaction that reduces yield and complicates product purification.

SCHEME 1



1: R_1=H, R_2=EtNHCO
3: R_1=EtNHCO, R_2=H
4: R_1=EtNHCO, R_2=EtNH

Previous work at Pharmacia showed that catalysis by CuCl permitted the ethyl isocyanate reaction to be run at rt with only 3 equiv of ethyl isocyanate.[2] With appropriate choice of phosphine or nitrogen ligands, the ratio of **1**/**3**/**4** can be varied to produce the desired product in abundance. Under optimum conditions (1:1 CuCl and Ph_3P), an 82:6:12 mixture of **1**/**3**/**4** was obtained. However, despite the moderation in reaction conditions with CuCl catalysis, conversion to product is low (about 80%) and the optimum product distribution and conversion are not much different from the uncatalyzed thermal reaction.

Methods for the preparation of *N*-acylureas are limited. Acylation of ureas[3] or carbodiimides[4] provides access to these types of compounds, but these approaches are limited in utility to compounds symmetrically substituted on the urea nitrogens since acylation of unsymmetrical ureas or carbodiimides gives mixtures of both regioisomeric products. This approach was used in the original synthesis of cabergoline and proceeds with poor selectivity.[1] *N*-Acylureas have also been obtained from the reactions of alkynyl-9-BBN derivatives with isocyanates,[5] from acylium salts with isocyanates,[6] and as byproducts in the formation of amides from carbanions and isocyanates.[7]

With increasing demand for cabergoline, safer and more efficient alternatives to the current chemistry were

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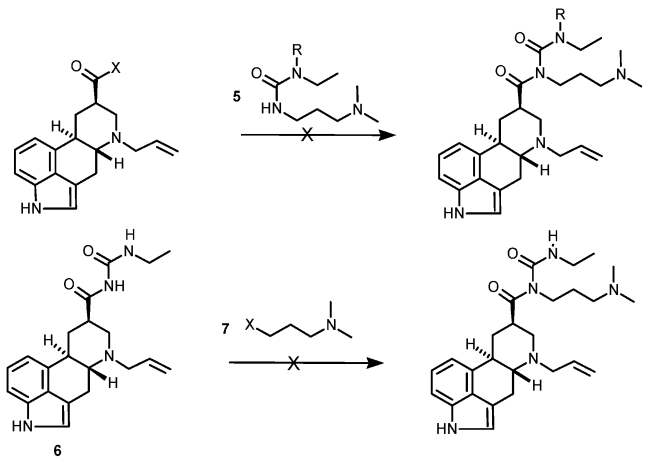
10.1021/jo0203847 CCC: $22.00
Published on Web 09/12/2002

SCHEME 2



investigated. A number of convergent methods for preparing the ureide functionality from cabergolinic acid or the methyl ester were examined, but these were universally unsuccessful. For example, a number of monoprotected unsymmetrical ureas (**5**, R = trityl, BOC, trifluoroacetyl) were prepared, but these were unreactive toward acylation with activated forms of cabergolinic acid (Scheme 2, X = Cl, OCO(O-isobutyl)) or cabergolinic acid methyl ester. Attempts at alkylating the ureide **6** (easily prepared from ethylurea, cabergolinic acid methyl ester, and potassium *tert*-butoxide) with various dimethylaminopropylamine derivatives (**7**, X = Cl, Br, OTs) proceeded poorly due to low reactivity of the ureide and the formation of multiple N- and O-alkylated products.

We now report a novel ethyl isocyanate-free method for the preparation cabergoline. The starting point for process development is cabergolinic acid methyl ester (**8**).[1] Amidation of the ester is accomplished by reaction with *N*,*N*-dimethylaminopropylamine in ethylene glycol at 100 °C with catalytic 2-hydroxypyridine[8] (Scheme 3). The amide **2** is obtained in 82% yield after extraction into methylene chloride followed by crystallization. These conditions are superior to the previous conditions used for this transformation, heating the ester with 10 equiv of dimethylaminopropylamine at 110 °C with acetic acid as a catalyst. Reaction under these conditions required >24 h for completion, and the product was isolated by precipitation from water. Without a catalyst, the amidation reaction is very slow and 2-hydroxypyridine was found to be a more efficient catalyst than acetic acid, allowing the reaction to be completed in <12 h. Crystallization from toluene yields an easily handled crystalline solid, rather than the slow-drying amorphous solid obtained by water precipitation.

Many of the problems with the exiting ethyl isocyanate process result from competing reaction with the indole nitrogen. Protection of the indole nitrogen would eliminate these competing pathways. A number of protecting groups were examined, and it was found to be best accomplished by protection as the *tert*-butyl carbamate. Reaction of amide **2** with di-*tert*-butyl dicarbonate in the presence of DMAP gives the BOC-protected indole **9** in essentially quantitative yield with high selectivity for reaction at the indole nitrogen.[9] Although amides are reported to react with BOC_2O under similar conditions,[10] even after refluxing with several equivalents of BOC_2O for extended times, only trace amounts of the products arising from acylation of the amide nitrogen are obtained. Silyl protection of the indole nitrogen was also investigated, but although both TMS and the more stable TIPS groups could be installed, they proved to be too labile in subsequent chemistry.

Extension of the amide side chain is done by deprotonation of **9** with NaHMDS followed by trapping the anion with phenyl chloroformate to yield the phenyl carbamate **10**. A survey of bases showed the highest conversion to product with NaHMDS or KHMDS. Conversions were significantly higher, and reactions were cleaner with these bases than with the other bases examined, *n*-butyllithium, LDA, or potassium *tert*-butoxide. Under the optimized conditions, 1.3 equiv of NaHMDS and 1.3 equiv of phenyl chloroformate are used for this conversion and give the product **10** in >95% yield.

The penultimate step, formation of BOC-cabergoline **11**, was the most problematic step in the synthesis. Reaction of **10** with ethylamine gives BOC-cabergoline **11** but also generates significant amounts of the ethylamide **12**. Little difference was seen between ethylamine and ethylamine HCl; the HCl salt is preferred since it is easier to control reaction stoichiometry. The amount of **12** formed is solvent dependent. Of the solvents examined (DMF, THF, CH_2Cl2, IPA, CH_3CN, Et_3N, and pyridine), very little ethylamide formation occurred in IPA or CH_3-CN. IPA proved to be the superior solvent since these reactions were homogeneous throughout and reactions were cleaner than in acetonitrile. Five equivalents of ethylamine HCl was the optimum amount, and larger amounts did not cause a faster reaction. Control reactions show that BOC-cabergoline does not react with ethylamine. Purification of the product obtained in 2-propanol proved to be unnecessary, and the crude product can be used directly in the deprotection reaction.

The deprotection was initially done with TFA at rt, but these conditions were not well tolerated by the substrate, producing tars on scale-up. No significant conversion to cabergoline was observed with weaker organic acids (acetic, dichloroacetic, trichloroacetic, and formic acid) at rt. Reactions run at 50 °C in methanol with anhydrous HCl gave product, but the reaction was not clean. It was found that the BOC group is readily removed by reaction with 1 N aqueous hydrochloric acid at 80 °C. Because of the basic nitrogen functionality, both **11** and cabergoline are fully soluble under these conditions. The reaction requires about 30−60 min for completion, and control reactions showed that cabergoline is stable to these conditions. No external nucleophile is needed to trap the *tert*-butyl cation that presumably forms in the deprotection; the large excess of water evidently serves this purpose. The product is then isolated by basification with ammonium hydroxide and extraction into ethyl acetate.

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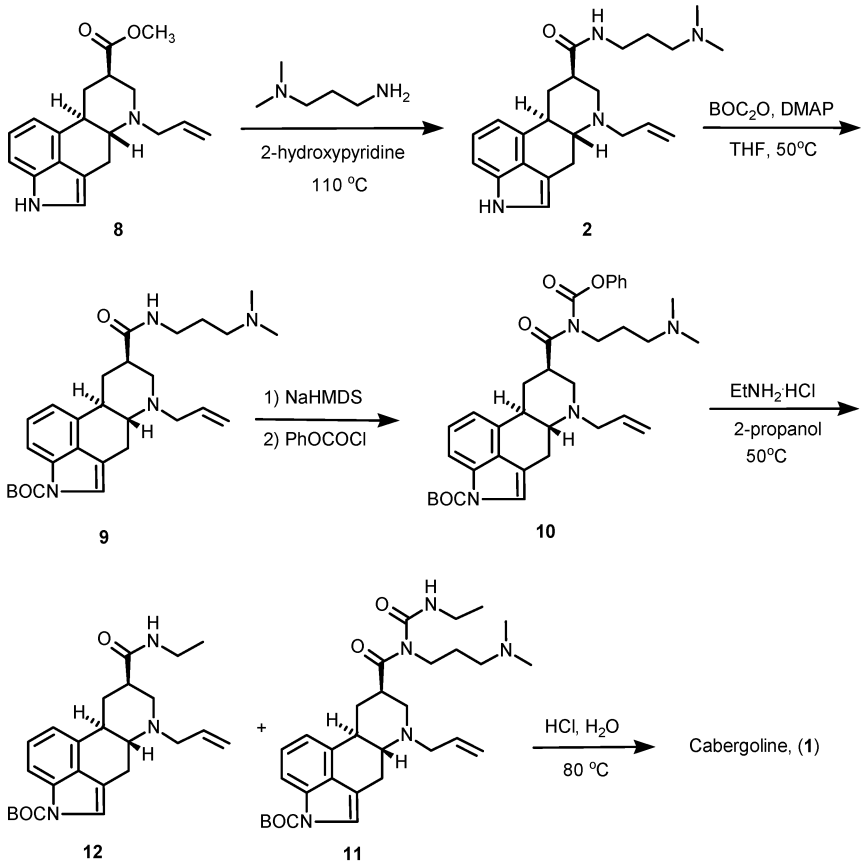
SCHEME 3



Chromatography on silica yields the purified product. Isolated crude yields are essentially quantitative, and yields after chromatography are about 78%.

An improved synthesis of cabergoline has been demonstrated. The current inefficient and hazardous ethyl isocyanate reaction has been replaced by a process involving formation of a phenyl carbamate followed by reaction with ethylamine to generate the *N*-acylurea. An efficient protection−deprotection sequence gives the product with high regioselectivity, and the entire process can be run without purification of the intermediates.

Experimental Section

(5*R*,8*R*,10*R*)-6-Allyl-*N*-[3-(dimethylamino)propyl]ergoline-8-carboxamide (2). Compound **8** (30.0 g, 96.6 mmol), 2-hydroxypyridine (2.76 g, 28.9 mmol), and *N*,*N*-dimethylaminopropylamine (49.37 g, 60.80 mL, 483.2 mmol) were combined and stirred at rt. Ethylene glycol (26.90 mL) was added, and the reaction was heated at 100 °C for 18 h. The mixture was cooled to 50 °C, and H_2O (100 mL) was added. CH_2Cl_2 (200 mL) was added to dissolve the product. The organic phase was separated and dried over Na_2SO_4. The CH_2Cl_2 was replaced with toluene by distillation. On cooling the product crystallized. After cooling to 0 °C, the product was filtered and dried on a nitrogen press (31.3 g, 85% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (m, 3H), 2.25 (s, 3H), 2.4−2.8 (m, 7H), 3.29 (m, 1H), 3.25 (d, J = 11.2 Hz, 1H), 3.41 (m, 3H), 3.45 (m, 4H), 3.6 (m, 1H), 5.19 (d, J = 10.2 Hz, 1H), 5.25 (d, J = 16.3 Hz, 1H), 5.98 (m, 1H), 6.90 (m, 2H), 7.16 (m, 2H), 7.59 (s, 1H), 8.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.46, 26.67, 30.99, 39.97, 40.53, 43.68, 45.45, 55.67, 56.48, 59.28, 63.57, 108.66, 111.66, 113.05, 117.86, 118.38, 123.00, 126.08, 132.91, 133.32, 133.65, 173.59.

***tert*-Butyl (5*R*,8*R*,10*R*)-6-Allyl-8-[[[3-(dimethylamino)-propyl]amino]carbonyl]ergoline-1-carboxylate (9).** Compound **2** (30.17 g, 79.3 mmol), di-*tert*-butyl dicarbonate (20.78 g, 95.1 mmol), and 4-(dimethylamino)pyridine (1.45 g, 11.90 mmol) were dissolved in THF (120 mL). The reaction was stirred at 40 °C for 2 h, EtOAc (240 mL) and H_2O (100 mL) were added, and the phases were separated. The organic layer was washed with saturated aqueous NaCl solution (20 mL) and H_2O (2 × 50 mL). The combined aqueous layers were extracted with EtOAc (1 × 25 mL). The ethyl acetate solutions were combined, dried over Na_2SO_4, filtered, and concentrated to a thick oil. Toluene (3 × 150 mL) was added to the oil and distilled to remove residual *tert*-butyl alcohol. The toluene was displaced with successive heptane distillations to give **9** as a viscous oil (34.94 g, 92% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (s, 12H), 2.24 (s, 6H), 2.40−2.88 (m, 8H), 3.21 (m, 1H), 3.38 (m, 4H), 3,54 (m, 1H) 5.19 (d, J = 10.2 Hz, 1H), 5.25 (d, J = 16.8 Hz, 1H), 5.95 (m, 1H), 7.05 (d, J = 7.6 Hz, 1H), 7.26 (m, 2H), 7.63 (s, 1H), 7.77 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.46, 26.31, 28.16, 30.89, 39.87, 40.13, 43.54, 45.42, 55.58, 56.34, 59.17, 63.05, 83.20, 113.02, 116.32, 116.83, 118.44, 119.19, 125.15, 128.33, 133.08, 133.43, 173.32; HRMS (FAB) *m*/*e* calcd for $C_{28}H_{40}N_4O_3$ 481.3178 $(M + H)^+$, found 481.3181 $(M + H)^+$.

***tert*-Butyl (5*R*,8*R*,10*R*)-6-Allyl-8-[[[3-(dimethylamino)-propyl](phenoxycarbonyl)amino]carbonyl]ergoline-1-carboxylate (10).** Compound **9** (34.94 g, 72.7 mmol) was dissolved in THF (175 mL) and cooled to −40 °C. A solution of NaHMDS in THF (1.0 M, 94.6 mL, 94.6 mmol) was added dropwise, and the reaction was stirred for 15 min at −40 °C. Phenyl chloroformate (11.86 mL, 94.6 mmol) was added slowly, and the reaction was stirred at −40 °C for 30 min and then warmed slowly to rt. EtOAc (350 mL) and H_2O (100 mL) were added, and the layers were separated. The organic layer was dried over Na_2SO_4, filtered, and concentrated to a thick dark red oil (57.1 g). The crude oil was used without purification in the ethylamine reaction. A portion of the product was purified by chromatography on silica eluting with acetone to give the product as a slightly yellow gum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (s, 10H),

1.89 (m, 2H), 2.24 (s, 6H), 2.37 (t, J = 7.1 Hz, 2H), 2.57 (m, 3H), 2.93 (m, 2H), 3.33 (m, 3H), 3.52 (m, 1H), 3.96 (m, 3H), 5.17 (d, J = 10.2 Hz, 1H), 5.24 (d, J = 17.3 Hz, 1H), 5.94 (m, 1H), 7.04 (d, J = 7.6 Hz, 1H), 7.23 (m, 5H), 7.42 (t, J = 7.6 Hz, 2H), 7.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.33, 26.98, 28.10, 28.18, 31.43, 39.82, 43.46, 43.62, 45.41, 55.48, 56.01, 57.08, 63.38, 83.15, 113.00, 116.51, 116.97, 118.08, 119.13, 121.40, 125.11, 126.31, 128.37, 129.51, 129.58, 129.62, 129.65, 133.14, 133.99, 150.10, 150.27, 153.05, 177.18; HRMS (FAB) *m/e* calcd for $C_{35}H_{44}N_4O_5$ 601.3390 $(M + H)^+$, found 601.3394 $(M + H)^+$. Anal. Calcd for $C_{35}H_{44}N_4O_5$: C, 69.97; H, 7.38; N, 9.33. Found: C, 70.07; H, 7.38; N, 9.37.

***tert*-Butyl (5*R*,8*R*,10*R*)-6-Allyl-8-[[[3-(dimethylamino)-propyl][(ethylamino)carbonyl]amino]carbonyl)ergoline-1-carboxylate (11).** Compound **10** (43.70 g, 72.7 mmol) was dissolved in 2-propanol (220 mL). Ethylamine HCl (29.7 g, 36.4 mmol) was added, and the reaction was heated to 50 °C. After 18 h, the excess ethylamine HCl was precipitated with EtOAc (440 mL) and collected by filtration. The organic layer was extracted with a 1:1 solution of H_2O and saturated NaCl (3 × 200 mL) and dried over Na_2SO_4. The yellow solution was concentrated to a thick oil (43.6 g) and used without purification in the next step. A portion of the product was purified by chromatography on silica eluting with acetone and then with 99:1 (v/v) acetone/TEA to give the product as a slightly yellow gum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, J = 7.1 Hz, 3H), 1.73 (s, 9H), 1.85 (m, 2H), 2.24 (s, 6H), 2.34 (m, 2H), 2.60 (m, 3H), 2.80 (m, 1H), 2.94 (m, 1H), 3.16 (d, J = 11.2 Hz, 1H), 3.3−3.5 (m, 7H), 3.83 (m, 2H), 5.2 (d, J = 10.2 Hz, 1H), 5.25 (d, J = 16.8 Hz, 1H), 5.95 (m, 1H), 7.05 (d, J = 7.1 Hz, 1H), 7.27 (m, 2H), 7.77 (s, 1H), 9.45 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.68, 26.32, 28.16, 29.23, 31.23, 35.39, 39.72, 42.18, 43.24, 44.84, 55.59, 56.01, 63.25, 83.18, 113.05, 116.32, 116.91, 118.36, 119.18, 125.15, 128.30, 132.94, 133.67, 150.05, 177.54; HRMS (FAB) *m/e* calcd for $C_{31}H_{45}N_5O_4$ 552.3549 $(M + H)^+$, found 552.3546 $(M + H)^+$.

***N*-[[(5*R*,8*R*,10*R*)-6-Allylergolin-8-yl]carbonyl]-*N*-[3-(dimethylamino)propyl]-*N*′-ethylurea (1).** Compound **11** (40.13 g, 72.7 mmol), H_2O (200 mL), and 1 M aqueous hydrochloric acid (182 mL, 182 mmol) were combined and heated to 80 °C for 1 h. EtOAc (300 mL) was added to the light yellow solution. The pH was adjusted to 10 with concentrated NH_4OH (30 mL). The organic phase was separated and extracted with H_2O (2 × 100 mL). The aqueous layer was extracted with EtOAc (1 × 100 mL), and the combined organic layer was dried over Na_2SO_4, filtered, and concentrated to an amorphous solid. Cabergoline was isolated in 94% yield (55% chemical yield overall from **8** in high purity (99 area % by HPLC): ^{1}H NMR ($CDCl_3$) δ 1.18 (t, J = 7.1 Hz, 3H), 1.76 (m, 2H), 1.85 (m, 2H), 2.23 (s, 6H), 2.34 (m, 2H), 2.53−2.84 (m, 4H), 2.98 (m, 1H), 3.17 (m, 1H), 3.29−3.44 (m, 4H), 3.55 (m, 1H), 3.83 (m, 2H), 5.19 (d, J = 10.2 Hz, 1H), 5.25 (d, J = 16.8 Hz, 1H), 5.95 (m, 1H), 6.87 (m, 2H), 7.14 (m, 2H), 8.88 (s, 1H), 9.45 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 26.61, 31.31, 35.41, 40.04, 42.23, 43.21, 44.93, 55.61, 56.10, 63.74, 108.7, 111.58, 113.10, 117.88, 118.36, 122.98, 126.02, 132.67, 133.31, 133.83, 177.89.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **1**, **2**, **9**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0203847