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Concise Synthesis of (±)-Cytisine via Lithiation of *N*-Boc-bispidine

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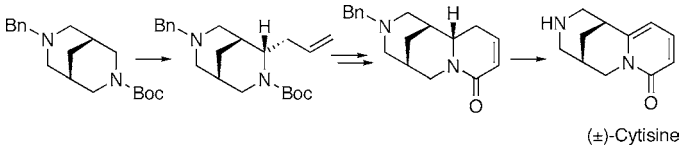
ABSTRACT



(±)-Cytisine has been synthesized in 19% overall yield via a six-step approach from commercially available materials. Key features of this new strategy are as follows: (i) initial construction of the bispidine core, (ii) lithiation–transmetalation–allylation of an *N*-Boc-bispidine, and (iii) a Pd/C-mediated dihydropyridone oxidation–*N*-debenzylation process.

(−)-Cytisine **1** is a naturally occurring lupin alkaloid that exhibits partial agonist activity at neuronal nicotinic acetylcholine receptors with specificity for the $\alpha4\beta2$ subtype.[1] Currently, there is much interest in the development of "cytisine-like" nicotinic agonists for the treatment of various CNS disorders and for assisting smoking cessation.[2−4] Indeed, Pfizer's drug, Varenicline, **2**, which is in late-stage phase III clinical trials as a smoking cessation drug, developed out of a cytisine-based drug discovery program (Figure 1).[4] The reported structure−activity relationship studies on cytisine analogues have focused on variation of the *N*-substituent as well as the C-9 and C-11 pyridone substituents.[2,3]

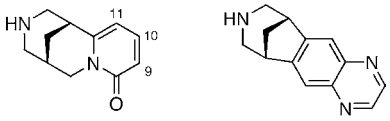


Figure 1.

To the best of our knowledge, C-10 pyridone analogues have not been prepared and evaluated as nicotinic agonists.

The interest in cytisine-based nicotinic agonists has led to renewed synthetic efforts in recent times. Following the efforts of van Tamelen,[5] Bohlmann,[6] and Govindachari[7] in the 1950s, five new syntheses of cytisine have been disclosed in the last five years (O'Neill,[8] Coe,[9] Lesma,[10] Gallagher,[11] and Honda[12]), including two asymmetric routes.[10,12] Interestingly, in all of the previous routes to cytisine, the bispidine core is crafted at a late stage in the synthesis. Thus, we sought

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(1) (a) Pabreza, L. A.; Dhawan, S.; Kellar, K. J. *Mol. Pharmacol.* **1991**, *39*, 9. (b) Heinemann, S. F.; Papke, R. L. *Mol. Pharmacol.* **1994**, *45*, 142. (c) Anderson, D. J.; Arneric, S. P. *Eur. J. Pharmacol.* **1994**, *253*, 261.

(2) (a) Canu Boido, C.; Sparatore, F. *Farmaco* **1999**, *54*, 438. (b) Nicolotti, O.; Canu Boido, C.; Sparatore, F.; Carotti, A. *Farmaco* **2002**, *57*, 469. (c) Canu Boido, C.; Tasso, B.; Boido, V.; Sparatore, F. *Farmaco* **2003**, *58*, 265.

(3) (a) Marrière, E. Rouden, J.; Tadino, V.; Lasne, M.-C. *Org. Lett.* **2000**, *2*, 1121. (b) Roger, G.; Lagnel, B.; Rouden, J.; Besret, L.; Valette, H.; Demphel, S.; Gopisetti, J.; Coulon, C.; Ottaviani, M.; Wrenn, L. A.; Letchworth, S. R.; Bohme, G. A.; Benavides, J.; Lasne, M.-C.; Bottlaender, M.; Dollé, F. *Biorg. Med. Chem.* **2003**, *11*, 5333.

(4) Coe, J. W.; Brooks, P. R.; Vetelino, M. G.; Wirtz, M. C.; Arnold, E. P.; Huang, J.; Sands, S. B.; Davis, T. I.; Lebel, L. A.; Fox, C. B.; Shrikhande, A.; Heym, J. H.; Schaeffer, E.; Rollema, H.; Lu, Y.; Mansbach, R. S.; Chambers, L. K.; Rovetti, C. C.; Schulz, D. W.; Tingley, F. D.; O'Neill, B. T. *J. Med. Chem.* **2005**, *48*, 3474.

(5) (a) van Tamelen, E. E.; Baran, J. S. *J. Am. Chem. Soc.* **1955**, *77*, 4944. (b) van Tamelen, E. E.; Baran, J. S. *J. Am. Chem. Soc.* **1958**, *80*, 4659.

(6) Bohlmann, F.; Englisch, A.; Ottawa, N.; Sander, H.; Weise, W. *Chem. Ber.* **1956**, *89*, 792.

(7) Govindachari, T. R.; Rajadurai, S.; Subramanian, M.; Thyagarajan, B. S. *J. Chem. Soc.* **1957**, 3839.

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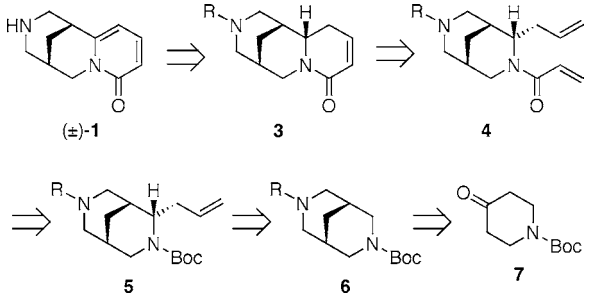
to develop a new strategy for cytisine synthesis where the bispidine would be constructed at the start of the synthesis (and subsequently elaborated to incorporate the pyridone functionality) and where there could be potential for the preparation of novel C-10 cytisine analogues. In this paper, we describe the successful implementation of such an approach to the synthesis of (±)-cytisine **1**. Our retrosynthetic analysis is summarized in Scheme 1.

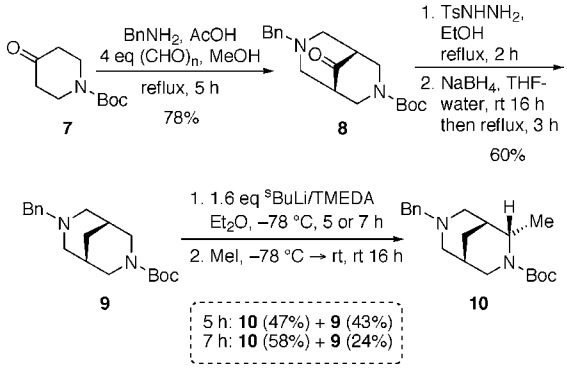
Scheme 1



It was envisaged that cytisine **1** would be generated from dihydropyridone **3** by oxidation (as precedented in Coe's and Lesma's syntheses[9,10]) and *N*-deprotection. Crucially, dihydropyridone **3** could be a key intermediate for the generation of C-10-substituted cytisine analogues. Ring-closing metathesis of diene **4** should produce **3** since similar metathesis reactions have been widely used to prepare *N*-heterocycles,[13] including a number of dihydropyridones.[14] Metathesis precursor **4** would be obtained from allylated *N*-Boc-bispidine **5**. One of the key steps in our proposed route is the allylation of *N*-Boc-bispidine (**6** → **5**). To achieve this, we planned to use *s*-BuLi/TMEDA-mediated lithiation of **6** and subsequent trapping, as precedented in our group for bispidine **6** (R = Me).[15] Finally, bispidines such as **6** can be prepared in two steps from *N*-Boc-piperidone **7** (double Mannich reaction then Wolff−Kishner-style reduction[16]).

To start with, *N*-Boc-bispidine **9** was prepared in two steps (47% overall yield) as outlined in Scheme 2. Double Mannich reaction of *N*-Boc-piperidone **7** gave ketone **8** in 78% yield.[16] Subsequent carbonyl group removal was best

Scheme 2



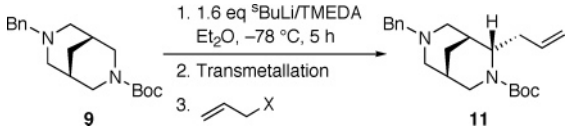
achieved using sodium borohydride reduction of the intermediate tosyl hydrazone, according to a literature method.[17] In this way, ketone **8** gave the required *N*-Boc-bispidine **9** in 60% yield.

Based on the precedent from Beak and Lee,[18] we have previously reported the successful lithiation-trapping of bispidine **6** (R = Me).[15] Our highest yielding reaction (71% yield) involved lithiation using *s*-BuLi/TMEDA in cyclopentane at −78 °C for 7 h followed by trapping with methyl iodide and this was subsequently exploited by Kozlowski et al. in the synthesis of a chiral diamine.[19] Hence, to assess the lithiation efficiency of the *N*-benzyl-*N*-Boc-bispidine **9**, we investigated its lithiation and alkylation with methyl iodide under different conditions (Scheme 2). In contrast to bispidine **6** (R = Me), Et_2O was preferred to cyclopentane as the solvent. With a 5 h lithiation time in Et_2O, methylated bispidine **10** was produced in 47% yield, together with 43% recovered bispidine **9**. An improvement in yield (58% of **10**) was seen on extending the lithiation time to 7 h but much less starting bispidine **9** (24%) was recovered. To account for the lower *overall* material recovery from the 7 h lithiation, we suspect that lithiation of *N*-Boc-bispidine **9** is relatively slow and, as a result, direct nucleophilic attack of *s*-BuLi onto the Boc carbonyl group becomes competitive.[20] Despite varying the diamine ligand, solvent and *s*-BuLi/diamine stoichiometry, the 58% yield of methylated bispidine **10** is our best yield for the lithiation-trapping of *N*-Boc-bispidine **9**. Adduct **10** was generated as a single diastereomer and the stereochemistry is assigned based on our previous work[15] and Kozlowski's X-ray crystal structure of a related methylated adduct.[19]

Confident in the knowledge that we could obtain at least ∼60% lithiation of *N*-Boc-bispidine **9**, we next addressed its allylation (Table 1). Direct allylation of the organolithium reagent generated from **9** with allyl bromide afforded only a 5% yield of a single diastereomer of allylated bispidine

(8) O'Neill, B. T.; Yohannes, D.; Bundesmann, M. W.; Arnold, E. P. *Org. Lett.* **2000**, *2*, 4201. For a formal synthesis of (±)-cytisine using this route, see: Nshimyumukiza, P.; Cahard, D.; Rouden, J.; Lasne, M.-C.; Plaquevent, J.-C. *Tetrahedron Lett.* **2001**, *42*, 7787.
(9) Coe, J. W. *Org. Lett.* **2000**, *2*, 4205.
(10) Danieli, B.; Lesma, G.; Passarella, D.; Sacchetti, A.; Silvani, A.; Virdis, A. *Org. Lett.* **2004**, *6*, 493.
(11) Botuha, C.; Galley, C. M. S.; Gallagher, T. *Org. Biomol. Chem.* **2004**, *2*, 1825.
(12) Honda, T.; Takahashi, R.; Namiki, H. *J. Org. Chem.* **2005**, *70*, 499.
(13) (a) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.
(14) (a) Park, S. H.; Kang, H. J.; Ko, S.; Park, S.; Chang, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2621. (b) Deiters, A.; Martin, S. F. *Org. Lett.* **2002**, *4*, 3243. (c) Chandra, K. L.; Chandrasekhar, M. Singh, V. K. *J. Org. Chem.* **2002**, *67*, 4630. (d) Rodríguez, S.; Castillo, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2002**, *58*, 1185.
(15) Harrison, J. R.; O'Brien, P. *Tetrahedron Lett.* **2000**, *41*, 6161.
(16) Huttenloch, O.; Laxman, E.; Waldmann, H. *Chem. Eur. J.* **2002**, *8*, 4767.
(17) Lesma, G.; Danieli, B.; Passarella, D.; Sacchetti, A.; Silvani, A. *Tetrahedron: Asymmetry* **2003**, *14*, 2453.
(18) (a) Beak, P.; Lee, W.-K. *Tetrhahedron Lett.* **1989**, *30*, 1197. (b) Beak, P.; Lee, W.-K. *J. Org. Chem.* **1993**, *58*, 1109.
(19) Phuan, P.-W.; Ianni, J. C.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 15473.
(20) Bailey, W. F.; Beak, P.; Kerrick, S. T.; Ma, S.; Wiberg, K. B. *J. Am. Chem. Soc.* **2002**, *124*, 1889.

Table 1. Lithiation−Allylation of *N*-Boc-bispidine **9**



9 11

entry	transmetalation[a]	Cu (equiv)	X (in allyl-X)	% yield of **11**[b]
1[c]	none		Br	5 (60)
2	A	1.0	Br	*d*
3	B	0.5	Br	*d*
4	B	1.0	Br	*d*
5	A	0.5	$OP(O)(OPh)_2$	23 (43)
6	A	1.0	$OP(O)(OPh)_2$	42 (36)
7	B	0.5	$OP(O)(OPh)_2$	15 (32)
8	B	1.0	$OP(O)(OPh)_2$	44 (32)
9[e]	B	1.0	$OP(O)(OPh)_2$	60 (32)

[a] Method A: (i) 1.3 equiv of $ZnCl_2$ in THF; (ii) 0.5 or 1.0 equiv of CuCN·2LiCl in THF. Method B: 0.5 or 1.0 equiv of CuCN·2LiCl in THF. [b] Isolated yield of **11** after chromatography with % yield of recovered starting bispidine **9** in parentheses. [c] 1.3 equiv of *s*-BuLi. [d] ^{1}H NMR spectrum of crude product showed only starting bispidine **9**. [e] Lithiation time = 7 h.

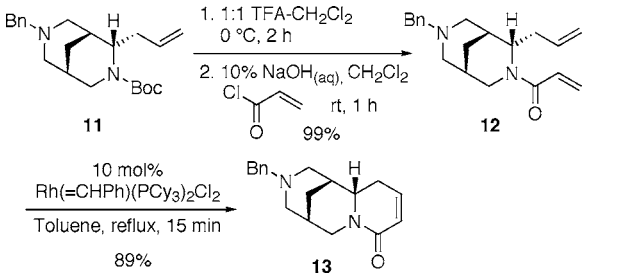
11 (entry 1), the stereochemistry of which was secured by an X-ray structure of **13** (see later).

Due to the lack of success with the organolithium reagent, our attention turned to transmetalation to organocopper reagents as pioneered by Dieter[21] (α-amino) and Taylor[22] (α-oxygen). Dieter's protocol converts the organolithium into the R_2CuLi or RCu(CN)Li reagent using 0.5 or 1.0 equiv of CuCN·2LiCl, respectively. In contrast, with the Taylor procedure, the organolithium is transformed into the RCu(CN)Li reagent via the organozinc species (using $ZnCl_2$ and then 1.0 equiv of CuCN·2LiCl). These three methods were uniformly unsuccessful for the organolithium derived from *N*-Boc-bispidine **9** with allyl bromide (entries 2−4).

Undeterred, we were attracted to a recent report from the Dieter group on the use of allyl phosphates for the allylation of α-amino organocuprates.[23] Pleasingly, use of allyl diphenyl phosphate with the Taylor (method A) and Dieter (method B) procedures (using either 0.5 or 1.0 equiv of CuCN·2LiCl) gave 15−44% yields of allylated bispidine **11** using a 5 h lithiation time (entries 5−8). As with our methylation studies (see Scheme 2), we recovered significant amounts of starting bispidine **9** (presumably due to incomplete lithiation). Our results indicate that the Taylor and Dieter procedures are comparable (compare entries 6/8) and that RCu(CN)Li (1.0 equiv CuCN·2LiCl) is the reagent of choice (compare entries 5/6 and 7/8). This may be a result of inefficient formation of the sterically more hindered R_2CuLi and/or reduced reactivity of this reagent compared to RCu(CN)Li. We prefer the direct transmetalation from lithium to copper (Method B) as it is experimentally more straightforward and, using the optimum conditions for high yielding methylation (i.e., 7 h lithiation time), we isolated allylated bispidine **11** in 60% yield (88% based on recovered starting material).

With a procedure for generating allylated bispidine **11** in place, we next prepared diene **12** (99% yield) via Boc deprotection and acylation (Scheme 3). Ring-closing metathesis of diene **12** using 10 mol % Grubbs' first-generation catalyst[13,14] gave an 89% yield of dihydropyridone **13** in just 15 min. This reaction is particularly efficient, presumably due to the equatorially disposed allyl group *and* the conformational rigidity of the bispidine. X-ray crytstallography of

Scheme 3



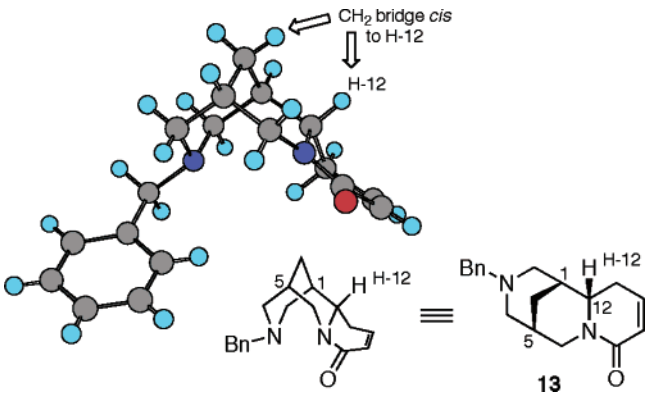


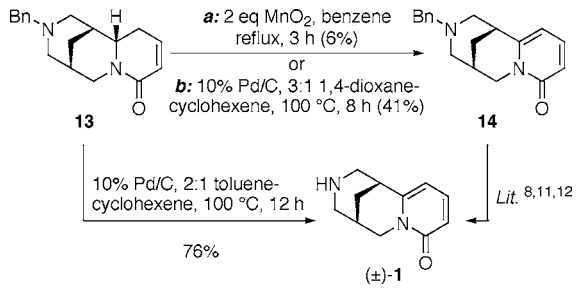
Figure 2.

dihydropyridone **13** (Figure 2) established its structure (and those of **11**/**12**).

At this stage, all that remained to complete the synthesis of cytisine was an oxidation-*N*-deprotection sequence. Taking our lead from Coe's route,[9] we attempted the oxidation of **13** to *N*-benzylcytisine **14** using MnO_2 in refluxing benzene. Unfortunately, only a 6% yield of *N*-benzylcytisine **14** was isolated (Scheme 4). Next, we investigated the DDQ-mediated oxidation procedure that Lesma[10] had successfully utilized on the *N*-Cbz-protected version of **13**. Disappointingly, however, no *N*-benzylcytisine **14** was produced under a variety of DDQ conditions. It is conceivable that the nucleophilic nitrogen lone pair in **13** is interferring with the MnO_2 and DDQ oxidations.

(21) Dieter, R. K.; Oba, G.; Chandupatla, K. R.; Topping, C. M.; Lu, K.; Watson, R. T. *J. Org. Chem.* **2004**, *69*, 3076.
(22) Papillon, J. P. N.; Taylor, R. J. K. *Org. Lett.* **2002**, *4*, 119.
(23) Dieter, R. K.; Gore, V. K.; Chen, N. *Org. Lett.* **2004**, *6*, 763.

Scheme 4



Therefore, with a view to *N*-benzyl hydrogenolysis followed by carbamate protection (and ultimate DDQ oxidation using Lesma's method[10]), we reacted dihydropyridone **13** with 10% Pd/C and $NH_4^+HCO_2^-$. Surprisingly, under these reducing conditions, we observed formation of reasonable amounts of *N*-benzyl cytisine **14**. Thus, we omitted the hydrogen source and included a large excess of cyclohexene, a good hydrogen acceptor. Under these conditions, we obtained a 41% yield of *N*-benzylcytisine **14**, thus completing a formal synthesis of (±)-cytisine **1** (Scheme 4). The use of Pd/C for aromatization has been known for some time[24] (including the formation of cytisine[6] and a quinolinone[25]) but it is not a commonly encountered method in total synthesis. Finally, further optimization involved a switch of solvent to toluene and an increased reaction time of 12 h. To our delight, under these conditions (10% Pd/C, 2:1 toluene−cyclohexene, 100 °C, 12 h), oxidation to the pyridone proceeded smoothly and was accompanied by *N*-debenzylation to afford (±)-cytisine **1** in 76% yield (Scheme 4). We presume that the cyclohexene acts first as a hydrogen acceptor for the oxidation to the pyridone and then acts as a hydrogen donor (for the *N*-benzyl hydogenolysis) as it is itself probably oxidized to benzene.

To summarize, we have completed a six-step synthesis of (±)-cytisine **1** in 19% overall yield. This is the first synthetic route in which the bispidine core of cytisine is constructed before pyridone elaboration. One of the key steps in our route is the unprecedented lithiation−transmetalation−allylation of *N*-Boc-bispidine **9**. Such allyation of **9** only proceeded satisfactorily using 1.0 equiv of CuCN·2LiCl for the transmetalation and allyl diphenyl phosphate as the electrophile. It is anticipated that dihydropyridone **13** will be a key intermediate in the generation of C-10 cytisine analogues.

Acknowledgment. We thank the BBSRC and Eli Lilly and Co. Ltd. for a CASE award (to D.S.) and Dr. A. C. Whitwood for the X-ray crystal structure.

Supporting Information Available: Experimental procedures, full characterization data, and copies of all ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) (a) Yukawa, K.; Fujii, T.; Saito, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 1548. (b) Maguire, J. A.; Goldman, A. S. *J. Am. Chem. Soc.* **1991**, *113*, 6706. (c) Crittendon, R. C.; Parsons, E. J. *Organometallics* **1994**, *13*, 2587.

(25) Ozturk, T.; McKillop, A. *Can. J. Chem.* **2000**, *78*, 1158.