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Studies toward Labeling Cytisine with [^{11}C]Phosgene: Rapid Synthesis of a δ-Lactam Involving a New Chemoselective Lithiation−Annulation Method

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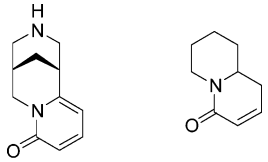
With the aim of the radiolabeling of cytisine, a potent agonist of nicotinic receptors, with [^{11}C]-phosgene, the rapid synthesis of a lactam model of our target has been studied. The key step of the δ-lactam formation is a new chemoselective lithiation−annulation method, under high dilution, of a suitable piperidinylcarbamoyl chloride. This precursor was obtained from (2-hydroxyethyl)-piperidine in a linear synthetic sequence involving a Corey−Fuchs olefination of the corresponding aldehyde, followed by a selective reduction, using a diimide equivalent, of an iodoalkyne into a (*Z*)-iodopropene piperidine. This alkene served as main precursor to study the cyclization according to several procedures using phosgene as the required carbonylating reagent.

Introduction

Recent studies have shown that nicotinic acetylcholine receptors (nAChRs) are involved in various physiological effects associated with nicotine. Moreover, the nAChR densities are altered in several neurodegenerative pathologies such as Alzheimer and Parkinson's diseases.[1] As a result, the in vivo quantitation of receptors using positron emission tomography (PET)[2] has attracted tremendous interest as a tool to investigate the role of the nicotinic system in these pathologies.[3] Several radioligands have been prepared to visualize nAChRs using PET (labeling with carbon-11, β^+ , $t_{1/2}$ = 20 min or fluorine-18, β^+ , $t_{1/2}$ = 110 min)[4] or using single photon emission computed tomography (SPECT, labeling with iodine 123, γ , $t_{1/2}$ = 13.1 h).[5] However, due to their toxicity or their high nonspecific binding, none of these ligands is ideally suited for imaging studies of the human brain.



1 **2**

FIGURE 1. (−)-cytisine **1** and model lactam **2**.

(−)-Cytisine **1** (Figure 1) is a quinolizidine alkaloid isolated from various plants of the *Leguminosae* family[6] and, in particular, from seeds of *Laburnum anagyroides*.[7] Owing to its nanomolar affinity[8] and its high selectivity toward the neuronal $\alpha_4\beta_2$ receptor subtypes,[9] (−)-cytisine **1** is often used as a reference ligand in the studies of the nicotinic neurotransmission. Its long half-life in vivo,[10] its ability to cross the blood−brain barrier,[11] its low nonspecific binding, and its slow clearance from the

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brain[12] in vivo compared to nicotine make cytisine a good candidate for PET studies. Prior to our interest for this molecule, only one analogue of cytisine, (*N*-^{11}C-methyl)-cytisine, was labeled with [^{11}C]CH_3I and studied in vivo.[4d] However, substitution on the secondary amino group of cytisine had a deleterious effect on the biological profile of this analogue since it displayed high nonspecific binding and a somewhat different biodistribution compared to the one of cytisine in baboon brains.

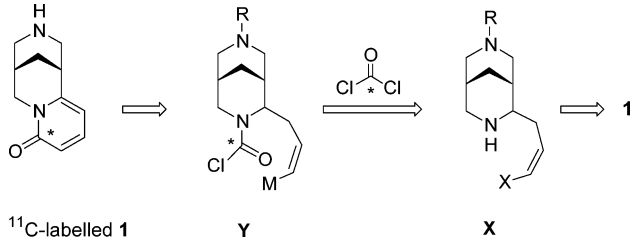
In our continuing interest for studying neurotransmission and in particular nAChRs, we undertook a project for labeling cytisine or some pyridone-substituted analogues for their use as radiotracers in PET studies. One part was devoted to the preparation of ^{18}F-labeled fluorinated analogues of cytisine, and we recently published some of this work.[13] The other part aims at labeling cytisine itself with carbon-11, and as pointed out several years ago,[12] this is a challenging task. The difficulty lies in the design of a rapid synthesis of [^{11}C]cytisine compatible with the limited number of labeled precursors and the structure of cytisine which lacks an easy-to-label position. Moreover, due to the short half-life of carbon-11, the introduction of the radioisotope must be rapid and carried out at the latest stage of the synthesis using a ^{11}C-labeled precursor directly available from the cyclotron ([^{11}C]carbon dioxide, [^{11}C]methane) or rapidly prepared from those ([^{11}C]iodomethane, [^{11}C]phosgene, ^{11}C-acids, and derivatives).[14] Considering these limitations, one structural feature of cytisine which attracted our attention was the carbonyl moiety of the pyridone ring. Therefore we focused our research on the use of phosgene as a possible labeled precursor for the introduction of a ^{11}C-carbonyl into cytisine.

This paper described our efforts toward the synthesis of the lactam **2** (Figure 1), a model compound for cytisine **1**. Different approaches based on the use of phosgene as the carbonylating reagent for building the lactam ring were studied. They involved the coupling of a (*Z*)-halogenoalkene piperidine either directly with phosgene or indirectly with a preformed carbamoyl chloride followed by an annulation.

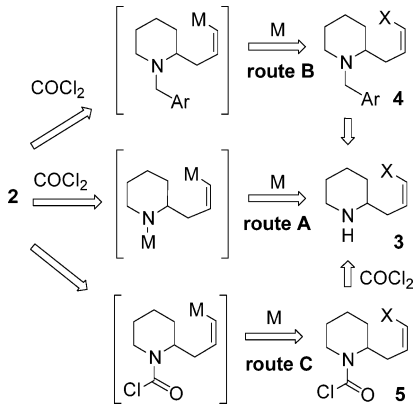
Results and Discussion

There are several methods for the synthesis of δ-lactams. Most of them include intramolecular aza annulation of imines or enamines,[15] catalyzed carbonylations,[16] ring-closure metathesis,[17] condensation of alkenamides with aryl aldehydes,[18] or aminolysis of a γ-lactone.[19]

SCHEME 1. Retrosynthetic Analysis for Labeling 1 (* = ^{11}C)



SCHEME 2. Envisaged Retrosynthetic Analyses for the Cyclization (M = Metal, X = Halogen)



These approaches required either α,β-unsaturated acid derivatives, carbon monoxide under pressure, or a preformed amide or lactone. Recently, it was shown that the carbamate protecting group of amines was reactive enough toward a carbanion to undergo an intramolecular cyclization.[20] All these substrates require too lengthy preparations to be usuable in short-lived isotope chemistry. To our knowledge, there are only two examples of carbonyl-labeled lactam synthesis.[21] However, they use [^{11}C]CO and a unique technology not available in our radiochemical facilities. Development of a synthetic strategy that could afford access to isotopically labelled lactams and more generally to δ-lactams is therefore highly desired.

In this context, our strategy for radiolabeling cytisine, depicted in Scheme 1, was centered on the use of phosgene, a precursor easily available in carbon-11. The key step is the double condensation of a properly functionalized precursor **X** with [^{11}C]phosgene and cyclization of anionic intermediate **Y**. The feasibility of this reaction was evaluated by synthesizing the model compound **2** starting from precursor **3** and was envisaged according to several procedures (Scheme 2). The first and the most obvious route (route A) involves a dianionic structure,

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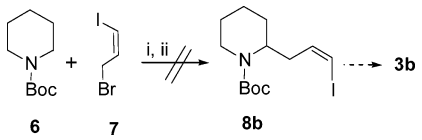
SCHEME 3. Directed Lithiation−Allylation of Boc-piperidine[a]



[a] Reagents and conditions: (a) *s*-BuLi, THF, −78 °C, with or without sparteine or TMEDA; (b) **7**, −78 to +20 °C, 15 h.

generated from precursor **3**, which reacts with phosgene. The second approach (route B) uses the *N*-benzylated precursor **4**, which undergoes an halogen−metal exchange reaction followed by condensation−debenzylation with phosgene. The final strategy tested (route C) starts from carbamoyl chloride **5**, prepared by reaction of phosgene with precursor **3,** and which reacts with the anion, formed via an halogen−metal exchange reaction, to cyclize into lactam **2**.

Synthesis of Precursor 3. A convergent approach was first tried in order to prepare the common precursor **3** (Scheme 3). It was based on Beak's methodology to functionalize *N*-Boc-piperidines via a directed lithiation α to nitrogen and subsequent alkylation with an electrophile.[22] All attempts to metalate *N*-Boc-piperidine **6** with *sec*-butyllithium (with or without sparteine, TMEDA, followed or not by a transmetalation step with CuCN·2LiCl[23]) then trapping the anion with (*Z*)-3-bromo-1-iodopropene[24] **7** failed to give the 2-alkylated piperidine **8b**, direct precursor of **3b** (X = I). Boc-protected piperidine **6** was quantitatively recovered with small amounts of alkene **7**.

Then we turned to a linear strategy starting from 2-(2-hydroxyethyl)piperidine **9** (Scheme 4). Protection of the secondary amine with a Boc group and Swern oxidation of the primary alcohol gave aldehyde **10** (80% overall yield). Using *o*-iodoxybenzoic acid (IBX),[25] the oxidation step was performed with a higher yield (95%) and under more convenient experimental conditions.[26] Thus, the crude aldehyde **10** was used without purification in the further steps. Wittig olefination[27] with bromomethyltriphenylphosphonium bromide afforded an inseparable mixture 70/30 of *Z*/*E* bromo alkenes **8a**. Therefore, to obtain selectively the (*Z*)-halogenoalkenes **8**, the following synthetic sequences were carried out.

Dibromo olefination[28] of aldehyde **10** furnished the dibromoalkene **11a**[29] or the diiodoalkene **11b** under modified conditions.[30] Selective reduction of the dibromide **11a** with tributyltin hydride catalyzed by palladium(0) afforded the (*Z*)-bromoalkene **8a** in 82% yield.[31] The same reduction conditions applied to diiodide **11b** led, under optimized conditions, to a mixture of products from which the expected (*Z*)-iodoalkene **8b** could be isolated with 39% yield. The moderate yield obtained in this case was due to over-reduction: reduced terminal alkene **13** was produced in 43% yield. Attempts to improve selectivity and yield for our substrate by changing the ligand of palladium [binap, dppp, dppf, P(*o*-tolyl)$_3$ instead of PPh_3][32] resulted mainly in the recovery of starting material **11b**. It is worth noting that we obtained the (*Z*)-iodoalkene **8b** from (*Z*)-bromoalkene **8a** via a recently developed copper-mediated substitution under Buchwald's conditions.[33] The reaction was completely stereoselective and could find wide application in the future. Treatment of dibromoalkene **11a** with *n*-butyllithium and quenching the reaction with iodine afforded the terminal iodoalkyne **12** with an average overall yield of 95%.[34] The same alkyne **12** was obtained with a moderate 40% yield in one step from aldehyde **10** using iodoform, triphenylphosphine, and an excess of *t*-BuOK according to a described procedure.[30] Moreover, purification of the product from phosphorus-based side products was quite difficult, and these conditions cannot be recommended here. Reduction of iodoalkyne **12** to (*Z*)-iodoalkene **8b** was performed in 73% yield with diimide using *o*-nitrobenzenesulfonylhydrazide (*o*-NBSH) in combination with Et_3N.[35] Finally, removal of the Boc group led to the target precursors **3a** and **3b**. Under the most efficient synthetic sequence, gram quantities of piperidines **3a** and **3b** were obtained with an overall yield of 61% and 53%, respectively.

Cyclization Studies Using Phosgene. To have a reference sample of lactam **2** we focused our research first on using a palladium cross-coupling reaction described for synthesizing amides from carbamoyl chlorides and tin derivatives.[36] However, the intramolecular version of this cross-coupling reaction required some adjustments. Attempts to transform bromoalkene piperidine **8a** into a (*Z*)-tributyltin alkene derivative failed [*t*-BuLi, THF, −78 °C followed by Bu_3SnCl or $(Bu_3Sn)_2$, $Pd(PPh_3)_4$, toluene, reflux]. The bulkiness of the tributyltin group probably prevented its introduction on a cis position of a double bond. Only the reduced terminal alkene **13** was detected in the crude mixture. Therefore, bromine−tin exchange was tried using a trimethyltin group. The palladium-mediated conditions ([$(Me_3Sn)_2$, $Pd(PPh_3)_4$], toluene, reflux) resulted in complete conversion as shown by the ^{1}H NMR of the crude product but purification on silica gel

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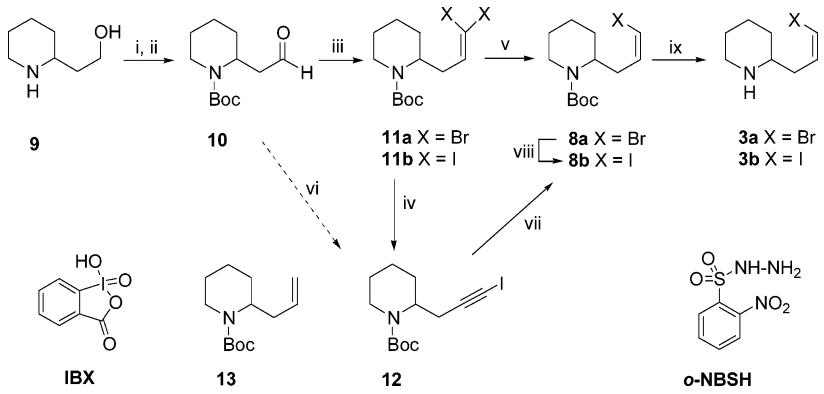
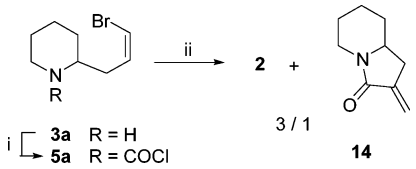
SCHEME 4. Synthesis of Lactam Precursors 3[a]



[a] Reagents and conditions: (i) $(Boc)_2O$, Et_3N, CH_2Cl_2, rt, 99%; (ii) IBX, EtOAc, 75 °C, 95%; (iii) **11a**: CBr_4, PPh_3, Et_3N, THF, −78 to rt, 87%. **11b**: CHI_3, PPh_3, *t*-BuOK, THF, rt, 68%; (iv) *n*-BuLi, THF, −78 to 0 °C then I_2, 95−99%; (v) *n*-Bu_3SnH, $Pd(PPh_3)_4$, toluene, rt, **8a**: 82%, **8b**: 39%; (vi) CHI_3, PPh_3, *t*-BuOK, THF, rt, 40%; (vii) *o*-NBSH, Et_3N, *i*-PrOH-THF, rt, 73%; (viii) NaI, CuI, $(CH_3NHCH_2-)_2$, *n*-BuOH, 120 °C, 47%; (ix) TFA, CH_2Cl_2, rt, **3a**: 92%, **3b**: 94%.

SCHEME 5. Stille−Kelly Type Cyclization for the Synthesis of Lactam 2[a]



[a] Reagents and conditions: (i) BTC, pyridine, CH_2Cl_2, rt, 86%; (ii) $Pd(PPh_3)_4$, $(Me_3Sn)_2$, toluene, 110 °C, 0.5 h, 39%.

proved to be difficult and did not allowed us to isolate the expected trimethyltin alkene, probably because of the known instability of the trimethyltin group on silica. To avoid any intermediate purification, we performed the cyclization using a procedure similar to the Stille−Kelly conditions[37] starting from carbamoyl chloride **5a** (Scheme 5): the labile trimethyltin group was generated in situ and coupled directly with the carbamoyl chloride group previously synthesized from precursor **3a**.

Under the best conditions tried, this procedure resulted in a mixture of two unseparable isomers in a 3/1 ^{1}H NMR ratio, the δ-lactam **2** and the α-methylene-γ-lactam **14** , respectively, in 39% total yield.[38] The formation of exomethylene lactam **14** could be explained by an intramolecular Heck reaction between the carbamoyl chloride group and the terminal alkene generated during the palladium-mediated halogen-exchange step.[39] Hexabutylditin was not a suitable reagent for this particular cyclization since only starting material **5a** was recovered. This confirmed our previous observation on the difficulty of exchanging a bromide by a tributyltin group on (*Z*)-bromoalkene bromopiperidine **8a**.

We next undertook the cyclization using phosgene or triphosgene (BTC),[40] its safer solid substitute, as the required reagent for the carbonylation step according to our initial strategies depicted in Scheme 2. Three different pathways were tested depending on the starting compound and Scheme 6 describes the most efficient conditions for each route leading to lactam **2**. The most simple procedure, route A, utilized bromo or iodopiperidines **3** as starting materials. It consisted in generating a dianionic intermediate **A** by simultaneous amine deprotonation and halogen−metal exchange steps with subsequent trapping by a carbonylating reagent. Double metalation was carried out at − 78 °C in THF or Et_2O using *t*-BuLi (3.5 equiv), with or without transmetalation ($MgBr_2$, CuCN·2LiCl), followed by the addition of a carbonyl equivalent (phosgene, triphosgene, carbon dioxide, or dimethyl carbonate). Small amounts (less than 10%, from ^{1}H NMR) of lactam **2** were detected only from piperidine **3b** when the transmetalation step using $MgBr_2$ was followed by trapping the anion by BTC. In the other cases, the major compound detected on the ^{1}H NMR of the crude product was carbamoyl chloride **15** bearing a dehalogenated double bond. GC−MS analyses of crude mixtures of these unsuccessful experiments confirmed the formation of product **15** which was independently synthesized from allyl piperidine **13**. This result suggests that the halogen−lithium exchange reaction occurred but the resulting anion was probably too unstable and was reprotonated before reacting with the carbonylating reagent. A further attempt to exchange iodine of piperidine **3b** with an excess of *i*-PrMgBr was unsuccessful.[41] Only starting material was recovered.

We then turned our efforts toward route B which takes advantage of a reaction recently developed in our laboratory for the synthesis of ^{11}C-carbamoyl chlorides from *N*-benzylamines.[42] According to this procedure, it should be possible to carry out a ring closure by cleaving the benzyl group of piperidines **4a**−**c** with the acid chloride generated by the reaction of the vinyl anion **B** with phosgene (Scheme 6). Piperidines **4**, readily available from **3**, were treated by *t*-BuLi (followed or not by a

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(38) ^{1}H NMR identification. (a) For compound **2**: Takatsu, N.; Ohmiya, S.; Otomatsu, H. *Chem. Pharm. Bull.* **1987**, *35*, 891−894. (b) For compound **14**: Mori, M.; Washioka, Y.; Urayama, T.; Yoshiura, K.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1983**, *48*, 4058−4067.

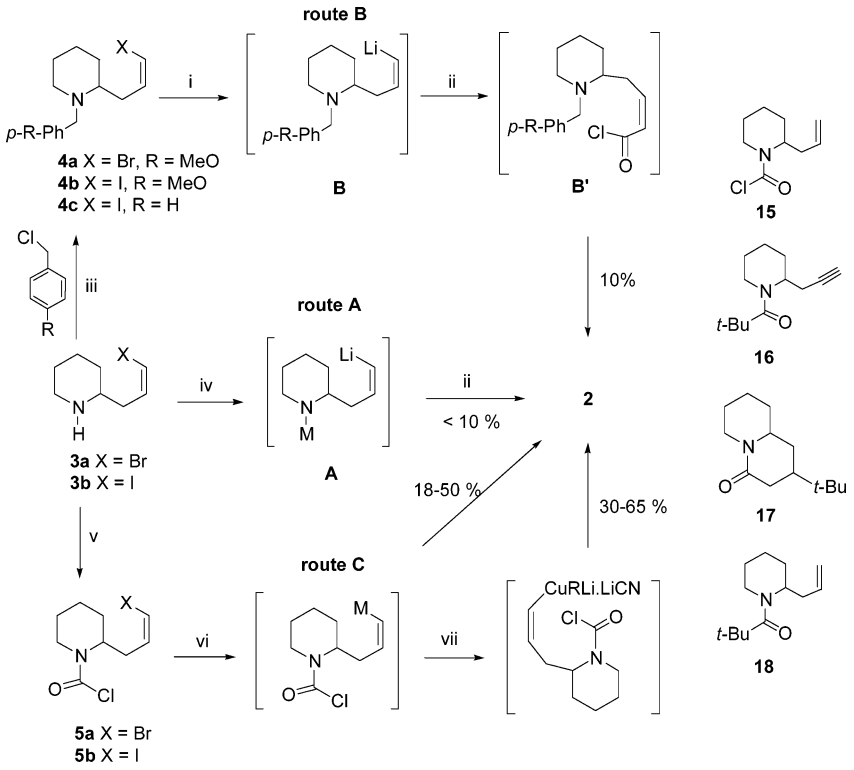
(39) Henin, F.; Muzart, J.; Pete, J.-P. *Tetrahedron Lett.* **1986**, *27*, 6339−6340.

(40) BTC, bistrichloromethyl carbonate.

(41) For a review on halogen−magnesium exchange using Grignard reagents, see: Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302−4320.

(42) Lemoucheux, L.; Rouden, J.; Ibazizene, M.; Sobrio, F.; Lasne, M.-C. *J. Org. Chem.* **2003**, *68*, 7289−7297.

SCHEME 6. Chemoselective Lithiation−Annulation Providing Lactam 2[a]



[a] Reagents and conditions: (i) *t*-BuLi, THF, −78 °C, 2 h; (ii) BTC, −78 °C to rt, 15 h; (iii) aq Na_2CO_3, CH_2Cl_2, rt, 15 h, 50−73%; (iv) *t*-BuLi, THF, −78 °C, 2 h then $MgBr_2$, 0.5 h; (v) BTC, Pyr, CH_2Cl_2, rt, 15 h, 86−92%; (vi) M, THF, 2 h, see Table 1 for details; (vii) RCuLiCN, −78 °C to rt, see Table 1 for details.

transmetalation step with CuCN·2LiCl or Lipshutz's thienylcyanocuprate[43]) and phosgene or BTC were used to trap the anion **B** as a putative acid chloride **B′**. Starting from iodoalkenes piperidine **4b** or **4c**, lactam **2** was isolated in a disappointing 10% yield following the conditions described in Scheme 6. As previously observed, the main compound of the reaction was the carbamoyl chloride **15**, suggesting again a competitive protodehalogenation. With bromoalkene piperidine **4a** the reactions led to complex mixtures of products, some of these containing an alkynyl group (characterized by ^{13}C NMR spectrum of the crude mixture) resulting probably from an elimination instead of the halogen−metal exchange reaction. This observation was confirmed by our last set of experiments. As expected, in all cases the debenzylation occurred when we added phosgene to trap the vinylic anion. Other conditions tried for the iodine−metal exchange included the use of Rieke's copper,[44] *i*-PrMgBr, and $(Neophy)_2CuLi$,[45] however, without success.

Last, we tried route C, which involved a cyclization similar to a Parham[46] reaction. There are only a few reports on the cyclization between a vinyllithium and a reactive electrophile.[47] However, to our knowledge, none of them have used a carbamoyl chloride group as the electrophilic counterpart in such a reaction. Carbamoyl chlorides **5** were conveniently synthesized from piperidines **3** (Scheme 6). Several reagents and conditions were tested to perform the halogen−metal exchange (lithium, magnesium, copper) and then to promote the cyclization onto the carbamoyl chloride moiety. The most representative results are summarized in Table 1.

The first conditions tried (entries 1 and 2) using magnesium metal to generate the anion at room temperature from the vinyl halide moiety in the presence of a carbamoyl chloride group provided lactam **2** in rather encouraging yields. These remarkable results (mainly entry 2) suggested that a Grignard reagent could be generated at room temperature in the presence of a carbamoyl chloride group. We anticipated that at low temperature (−78 °C or below), *t*-BuLi would not react with a carbamoyl chloride group under the conditions used. Nevertheless, treatment of bromoalkene **5a** with *t*-BuLi at −120 °C did not produce any lactam **2** (entry 3). Instead, alkyne **16** was isolated as the main product in 41% yield from a complex mixture. Because of a difficult purification, this compound was only partially characterized.[49] Moreover, addition of 2 equiv of *t*-BuLi on **5a** at −120 °C, as recommended for lithiation of (*Z*)-bromoalkenes,[50] did not perform the bromine−lithium exchange step. An elimination reaction leading to a terminal alkyne followed by the addition of one molecule

(43) Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, *285*, 437−447.
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(45) Piazza, C.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 3263−3265.
(46) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300−305.
(47) Clayden, J. In *Organolithiums: Selectivity for Synthesis*; Pergamon: Amsterdam, 2002; pp 284−285.
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(49) See the Experimental Section and the Supporting Information for spectral data of alkyne **16**.
(50) Neumann, H.; Seebach, D. *Tetrahedron Lett.* **1976**, 4839−4842.

TABLE 1. Chemoselective Lithiation−Annulation Conditions Providing Lactam 2 (Route C)

entry	substrate	reagent temp[a] (°C)	transmetalation[b]	[M][c]	yield[d] (%)
1	**5a**	Mg (30 to 40)	n.a.	0.03	18
2	**5b**	Mg (30 to 40)	n.a.	0.03	40
3	**5a**	*t*-BuLi (−120)	n.a.	0.02	0[f]
4	**5b**	*t*-BuLi (−78)	n.a.	0.05	0[g,k]
5	**5b**	*t*-BuLi (−78)	2-thienylCuLiCN	0.05	0[h,k]
6	**5b**	*t*-BuLi (−78)	2-thienylCuLiCN	0.025	30[i,k]
7	**5b**	*t*-BuLi (−78)	$TMSCH_2CuLiCN$[48]	0.0025	47[i,k]
8	**5b**	*t*-BuLi (−78)	2-thienylCuLiCN	0.0025	59[i,k]
9	**5b**	*t*-BuLi (−78)	2-thienylCuLiCN	0.0012	60[i,k]
10	**5b**	*t*-BuLi (−90)	2-thienylCuLiCN[e]	0.0025	65[j,k]
11	**5b**	*t*-BuLi (−90)	n.a.	0.005	50[j,k]

[a] Halogen-exchange step in THF for 2 h. [b] n.a.: not applicable; when applicable, the transmetalation was carried out at −78 °C and the temperature reached rt over 15 h. [c] Initial concentration of starting material. [d] Isolated yield. [e] The reaction temperature reached rt in 2 h after transmetalation. [f] Alkyne **16** was isolated as the major product with a 41% yield. [g] Compound **17** was isolated as the major product with a 48% yield. [h] Compound **15** was detected by ^{1}H NMR and GC−MS analyses as the major product. [i] With 15−20% of product **17**. [j] With 5−10% of product **17**. [k] Compound **18** was detected by GC−MS analysis of the crude mixture (less than 10%).

of *t*-BuLi on the carbamoyl chloride moiety generated the amide group. When starting from iodopiperidine **5b**, a peculiar lactam **17** was isolated as the major product with a 48% yield, but no trace of compound **2** (entry 4). We are currently investigating the mechanism of this interesting anionic carbocyclization leading to **17**.[51] Lithiation of **5b** followed by transmetalation with copper (entry 5) still did not afford the expected lactam **2** but mainly alkene **15** identified by ^{1}H NMR and GC−MS analyses of the crude mixture. As previously discussed, this showed that the iodine−lithium exchange step occurred, but for unknown reasons, the resulting anion was either unreactive or rapidly reprotonated. However, when performing the same experiment after diluting twice more, lactam **2** was isolated with a significant 30% yield along with 15−20% of lactam **17**, unseparable from lactam **2** (entry 6). Therefore, while increasing the dilution, the yield of the cyclization reached 60% (entry 7−9), lactam **2** was still contaminated with 15−20% of side product **17**. To decrease the amount of **17**, the iodine−lithium exchange was carried out at −90 °C followed by a transmetalation at −78 °C with Lipshutz cyanocuprate. Thus, the highest yield (65%) with 5−10% of lactam **17**, was obtained under high dilution (2.5 mM) and rapid warming (2 h) of the reaction temperature after the transmetalation (entry 10). Interestingly, the expected cyclization leading to lactam **2** occurred well with a lithiated anion, however under high dilution (entry 11). In all reactions starting with iodopiperidine **5b**, we detected by GC−MS analysis of the crude mixtures small amounts (less than 10%) of a pivaloylpiperidine **18** (characterized by its MS spectrum), resulting from the addition of *t*-BuLi on the carbamoyl chloride group. This side reaction generating amide **18** could certainly be avoided by lowering the temperature (−100 °C or below)[52] or by using mesityllithium as a chemoselective reagent for a halogen−lithium exchange reaction.[53] Finally, an attempt to exchange iodine of piperidine **5b** with an excess of *i*-PrMgBr was unsuccessful and starting material was recovered. Evidently from these results, the countercation did not seem to have a major effect on the cyclization whereas high dilution was the main parameter to achieve this new version of the Parham reaction. This original annulation strategy, involving the selective generation of a lithioalkene besides a carbamoyl chloride, allowed for a direct access to α,*β*-unsaturated lactams.

(51) At the moment *we do not believe* that compound **17** could result from a 1,4 addition of remaining *t*-BuLi on lactam **2**.

(52) For an example of the effect of the temperature on a chemoselective lithiation, see: Parham, W. E.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 1187−1191.

Conclusion

On our way to address the challenge of radiolabeling of (−)-cytisine **1** with short-lived isotopes, we have developed a new lactam annulation on a model compound (lactam **2**) involving the chemoselective lithiation of a bifunctional precursor, prepared according to a seven-step linear synthesis. Of particular interest were the efficient conversion of an iodoalkynyl piperidine selectively to a (*Z*)-iodoalkene using *o*-NBSH as a diimide equivalent and the bromo-to-iodoalkene copper-mediated substitution. The strategy we have developed uses phosgene (or an equivalent) as the reagent to introduce the carbonyl part of the lactam. The new annulation method disclosed here is the first example of a successful halogen−lithium (magnesium) exchange in the presence of a carbamoyl chloride, followed by its intramolecular condensation. High dilution of the carbamoyl chloride was the key factor to achieve the cyclization, conditions required in chemistry using carbon isotopes. This procedure represents a valuable alternative to the carbon monoxide palladium-catalyzed chemistry, especially for six-membered ring lactams. Moreover, it provides a novel access to the preparation of functionalized organometallic compounds, nucleophilic intermediates which are of increasing interest for modern organic synthesis. This methodology will be applied to the labeling of (−)-cytisine **1** with [^{11}C]phosgene and elucidation of the mechanism leading to the formation of lactam **17** is currently underway.

Experimental Section

1,6,7,8,9,9a-Hexahydro-4*H*-quinolizin-4-one (2).[38] General procedure for entries 1 and 2, Table 1: To a magnesium (0.20 g, 8.3 mmol, 25 equiv) suspension in dry THF (3 mL) under nitrogen was added an iodine crystal followed by 1,2-dibromoethane (0.18 g, 0.9 mmol, 3 equiv) at rt. When the temperature increased, a solution of 1,2-dibromoethane (0.12 g, 0.6 mmol, 2 equiv) and carbamoyl chloride **5b** (0.10 g, 0.3 mmol, 1 equiv) in THF (5 mL) was slowly added during 10 min. After 1 h at rt, the reaction mixture was hydrolyzed with a saturated NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated. Purification by flash chromatography on silica gel (AcOEt/Pentane 5/1) afforded 20 mg of lactam **2** as a colorless oil (slightly contaminated by impurities).

General procedure for entries 5 to 10, Table 1: To a cold (−78 or −90 °C, see Table 1) solution of carbamoyl chloride **5b** (0.156 g, 0.5 mmol, 1 equiv) in THF (see Table 1 for concentration) under nitrogen was slowly added *t*-BuLi (1.7 M in pentane, 0.65 mL, 1.1 mmol, 2.2 equiv). The mixture was

(53) Kondo, Y.; Asai, M.; Miura, T.; Uchiyama, M.; Sakamoto, T. *Org. Lett.* **2001**, *3*, 13−15.

stirred for 2 h. When applicable, a lithium 2-thienylcyanocuprate solution (0.25 M in THF, 2 mL, 0.5 mmol, 1 equiv) was added at −78 °C, and the temperature was allowed to reach rt (overnight or in 2 h). The reaction mixture was hydrolyzed with a saturated NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated to give lactam **2** after purification by chromatography, unseparable from small amounts of amide **17**. ^{1}H NMR: δ = 1.25−1.80 (m, 6H), 2.05−2.20 (m, 1H), 2.35−2.50 (m, 2H), 3.25−3.50 (m, 1H), 4.42 (dd, J = 11.6, 1.5 Hz, 1H), 5.90 (ddd, J = 9.8, 2.3, 1.5 Hz, 1H), 6.48 (ddd, J = 9.8, 5.0, 3.4 Hz, 1H). ^{13}C NMR: δ = 24.0, 24.8, 31.1, 33.4, 43.0, 54.8, 124.7, 138.0, 165.6. IR (NaCl): 3456, 2936, 2860, 1668, 1636, 1618, 1468, 1442, 1274, 824 cm^{-1}. MS (EI) *m*/*z*: 151 (M, 94), 136 (12), 122 (33), 108 (10), 84 (100). HRMS (EI): calcd for $C_9H_{13}NO$ 151.0997, found 151.1002.

1-[2-(2-Propenyl)piperidin-1-yl]-2,2-dimethyl-1-propanone (16). To a cold (−120 °C) solution of carbamoyl chloride **5a** (0.270 g, 1.01 mmol, 1 equiv) in a 2/2/1 mixture of THF/Et_2O/pentane (50 mL) under nitrogen was slowly added *t*-BuLi (1.7 M in pentane, 1.3 mL, 2.23 mmol, 2.2 equiv). The mixture was stirred for 2 h at −115 °C or below. Then the temperature was allowed to reach rt overnight, and the reaction mixture was hydrolyzed with a saturated NH_4Cl solution and extracted with CH_2Cl_2. Purification by flash chromatography on silica gel (AcOEt/pentane 3/2) afforded 0.085 g of amide **16** (41% yield) as a colorless oil (slightly contaminated by impurities). ^{1}H NMR: δ = 1.28 (s, 9H), 1.30−2.20 (m, 5H), 1.80−2.00 (m, 2H), 2.30−2.70 (m, 2H), 2.85 (br s, 1H), 4.18 (br d, J = 12.8 Hz 1H), 4.78 (br s, 1H). ^{13}C NMR: δ = 18.7, 19.5, 25.5, 26.6, 28.4, 38.8, 49.6, 52.4, 70.1, 81.0, 176.5; MS (CI) *m*/*z*: 208 (M + 1, 100), 168 (12). GC analysis: retention time, 10.3 min (T_{inj}, 230 °C, Col., 50 °C for 1 min, then +15 °C/min until 250 °C).

2-(Dimethylethyl)octahydro-4*H*-quinolizin-4-one (17). To a cold (−78 °C) solution of carbamoyl chloride **5b** (0.156 g, 0.5 mmol, 1 equiv) in THF (10 mL) under nitrogen was slowly added *t*-BuLi (1.7 M in pentane, 0.65 mL, 1.1 mmol, 2.2 equiv). The mixture was stirred for 2 h, and then the temperature was allowed to reach rt in 2 h. The reaction mixture was hydrolyzed with a saturated NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated to give, after purification by flash chromatography (heptane/EtOAc: 1/1) on silica gel, 0.050 g of lactam **17** (48% yield). ^{1}H NMR: δ = 0.87 (s, 9H), 1.25−1.67 (m, 8H), 1.75−2.20 (m, 2H), 2.40−2.49 (m, 2H), 3.38−3.41 (m, 1H), 4.73 (dq, J = 12.8, 2.0 Hz, 1H). ^{13}C NMR: δ = 25.4, 25.5, 26.9, 30.1, 31.7, 32.8, 34.8, 39.0, 43.7, 56.6, 169.2. IR (NaCl): 3018, 2964, 2940, 2870, 1618, 1474, 1216 cm^{-1}. MS (EI) *m*/*z*: 209 (M, 100), 195 (86), 152 (68), 138 (10), 124 (18), 97 (47), 84 (64).

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Supporting Information Available: General experimental conditions; preparation, characterization, ^{1}H NMR, and ^{13}C NMR spectra for compounds **3a**,**b**, **4a**−**c**, **5a**,**b**, **8a**,**b**, **11a**,**b**, **12**, **13**, and **15**; ^{1}H NMR and ^{13}C NMR spectra for compounds **2**, **16**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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