ORGANIC
LETTERS

2007
Vol. 9, No. 1
153−156

Diastereoselective Conjugate Addition of Organocuprates to 3,4-Dimethyl-5,6-dihydro-2(1*H*)-pyridinones. A Concise Synthesis of *trans*-3,4-Dimethyl-4-phenylpiperidines

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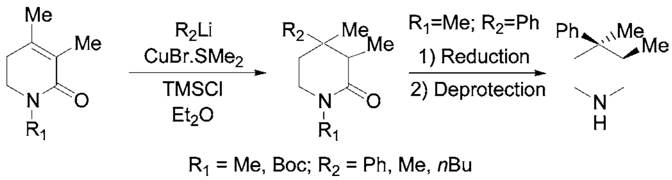
Received November 6, 2006

ABSTRACT



Conjugate addition of aryl or alkyl cuprates to 3,4-dimethyl-5,6-dihydro-2(1*H*)-pyridinones led to diastereoisomerically pure 3,4,4-trisubstituted 2-piperidinones in 39–78% yields. The yields and the diastereochemistry of piperidinones depended on both the *N*-protecting group and the organocuprate. Reduction then deprotection of the *trans*-3,4-dimethyl-4-phenyl product provided the corresponding piperidine, analogue of a key precursor of opioid receptor antagonists.

The *trans*-3,4-dimethyl-4-phenylpiperidines such as LY-255582,[1] LY246736,[2] and JDTic[3] (Figure 1) are a unique class of compounds exhibiting pure opioid antagonist activity that may prove useful in the treatment of obesity, psychosis, and depression, as well as opioid and cocaine abuse and other central nervous system disorders. It was demonstrated that the stereochemical configuration at the C-3 and C-4 positions of the piperidine ring is critical for the intrinsic antagonist activity, whereas the nature of the *N*-substituent affects the binding potency and the selectivity toward μ, δ, and κ opioid receptor subtypes.[1−4] Therefore, piperidine **A** is a versatile molecular framework for the development of pharmacotherapeutic agents and molecular tools in the study of the physiological function of the highly complex opioid receptor system.

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10.1021/ol062708+ CCC: $37.00

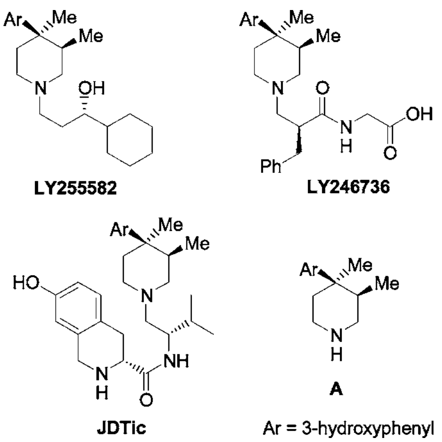
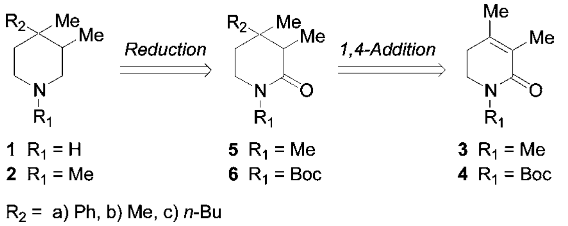


Figure 1. Opioid receptor antagonists.

The trans-diaxal relationship between the two methyl groups is a major challenge in the preparations of the piperidine **A**. An initial approach involved the reduction of the corresponding 2,3-enamine, but only moderate selectivity was achieved in controlling the relative stereochemistry of the C3-methyl group.[1,5] A regio- and stereospecific metalloenamine generation-methylation sequence from the 3,4-disubstituted 1,2,3,6-tetrahydropyridine was then developed as an alternative strategy.[3,6,7] However, the multistep synthesis required for the obtention of the starting tetrahydropyridine and the introduction of the 4-aryl group rather early in the reaction scheme make this route unconvenient for the synthesis of the target compound **A** and aryl-modified analogues.

The conjugate addition of alkyl or aryl cuprates to α,*β*-unsaturated lactams has previously proved to be a useful diastereoselectively controlled synthesis of *trans*-3,4-disubstituted piperidinones.[8] This latter process followed by reduction provided the corresponding piperidines.[8a,b,d] Herein, we report that trisubstituted piperidines **1** and **2**, analogues of the intermediate **A**, can be obtained according to a concise synthesis highlighted by a 1,4-addition of organocuprates to 3,4-dimethyl-5,6-dihydropyridinones[9] **3** and **4** (Scheme 1).

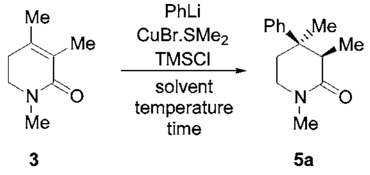
Scheme 1. Strategy through a Conjugate Addition



To our knowledge, there is no precedent for the conjugate addition of an organocuprate to a α,*β*-disubstituted-α,*β*-unsaturated lactam.

α,*β*-Unsaturated lactams are known to be poor Michael acceptors, and 3,4-disubstituted piperidinones were always obtained from substrates bearing at C3 an alkoxycarbonyl group mainly used as an electron-withdrawing substituent for enhancing the reactivity of the conjugated system.[8] Moreover, it is noteworthy that the organometallic reagent (alkyl- or aryllithium, magnesium bromide, zinc, or aluminium) was usually used in large amounts (2−10 equiv) compared to the lactam.[8] We first decided to check the viability of the proposed strategy starting from the nonactivated *N*-methyldihydropyridinone **3** and phenyl cuprate. Phenyl cuprate was formed in situ from phenyllithium (preferred to phenylmagnesium bromide)[8d] and was used in 2.5- to 10-fold excess compared to lactam **3**. Optimization of the conjugate addition conditions focused on copper sources, additives, solvent, temperature, and reaction time. After examining a number of cuprate reagents, we found that the desired 1,4-addition was best accomplished with the lower order homocuprate prepared from phenyllithium (10 equiv) and CuBr·SMe$_2$ (5 equiv) under the influence of

Table 1. Optimization of the Conjugate Addition to Dihydropyridone **3**[a]



entry	PhLi (equiv)	TMSCl (equiv)	solvent	*T* (°C)	time (h)	yield (%)
1	10	3.2	THF	−15	72	*b*
2	10	15	THF	−15	18	*b*
3	5	3.2	Et$_2$O	−15	16	*b*
4	10	3.2	Et$_2$O	−15	2	16[c]
5	10	3.2	Et$_2$O	−15	16	24[c]
6	10	12	Et$_2$O	−15	72	26[d]
7	10	3.2	Et$_2$O	−15 then rt	6 then 12	33[d]
8	10	3.2	Et$_2$O	0	18	58[d]

[a] CuBr·SMe$_2$ (5 equiv). [b] The dihydropyridinone **3** was recovered in 76−85% yield. [c] The only side product was the dihydropyridinone **3**. [d] No dihydropyridinone **3** was recovered; unidentified degradation products were obtained as byproducts.

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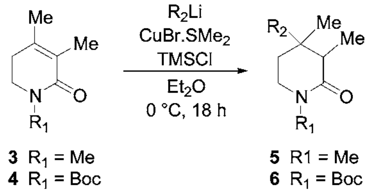
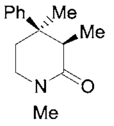
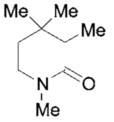
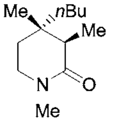
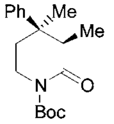
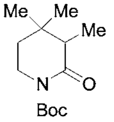
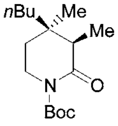
TMSCl catalysis[10] in Et_2O (Table 1). The use of CuBr and CuI in combination or not with $BF_3 \cdot OEt_2$ or TMSCl failed (data not presented). The lactam **3** was found totally inert in THF[11] (entries 1,2) and at temperature below −40 °C (data not shown). The piperidinone **5a** was obtained in poor yield when the reaction was carried out at −15 °C even with an extended reaction time (entries 3−7). The yield in **5a** was increased to 58% by raising the temperature to 0 °C (entry 8).

We then examined the 1,4-addition of methyl and *n*-butyl cuprate under the conditions previously determined and compared the reactivity of the lactams **3** and **4** in the preparation of piperidinones **5** and **6a−c** (Table 2). Despite the greater electron-withdrawing ability of the Boc group that would render the reactive *β*-carbon more electrophilic,[8g] no significant improvement in phenylcuprate addition yield was observed starting from the *N*-Boc lactam **4** instead of the *N*-methyl compound **3** (entry 1 vs 4). For the reactions with methyl and *n*-butylcuprate, the use of **4** rather than **3** led to a considerable reduction in the yield (entries 2 vs 5, 3 vs 6). The *N*-methyl piperidinones **5a−c** were obtained in yields ranging from 58 to 78%, whereas the *N*-Boc analogues **6a−c** were isolated in only 39−60% yields. In the *N*-methylpiperidinones series, alkyl cuprates were found to be more reactive than aryl cuprates with a reactivity order as follows: methyl > *n*-butyl > phenyl. The reactivity order was totally opposite in the *N*-Boc lactams series as reported for the synthesis disubstituted piperidinones.[8f] It is reasonable to assume that the *N*-methyl compounds were more stable in the reaction medium than the *N*-carbonyl analogues and led to reduced amounts of degradation products. Degradation of the *N*-Boc-piperidinones was greater when the cuprate was reactive.

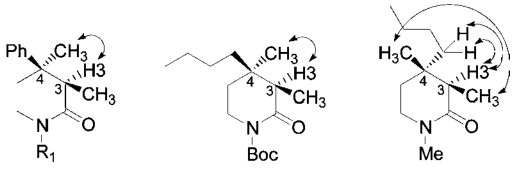
Table 2. 1,4-Addition of Organocuprates to Dihydropyridones **3** and **4**[a]



entry	substrat	R_2Li	product		yield (%)
1	**3**	PhLi		**5a**	58
2	**3**	MeLi		**5b**	78
3	**3**	*n*-BuLi		**5c**	66
4	**4**	PhLi		**6a**	60
5	**4**	MeLi		**6b**	39
6	**4**	*n*-BuLi		**6c**	54

[a] R_2Li (10 equiv), $CuBr \cdot SMe_2$ (5 equiv), TMSCl (3.2 equiv).

In all cases, the selectivity was totally controlled as only one diastereoisomer was obtained. The stereochemistry was assigned by NOESY experiments (Figure 2) and found to be dependent on the nature of the cuprate and of the *N*-protecting group. The stereoisomers **5a** and **6a** obtained for the reactions with phenyl cuprate displayed the two methyl groups in antiperiplanar position whatever the *N*-protecting group. Indeed, NOE effect was clearly observed in the structure **5a** between the protons of the methyl group at C4 (s, 1.36 ppm) and H3 (m, 2.60−2.70 ppm). Although visible, this NOE effect was more difficult to assign for the piperidinone **6a** due to the very closed NMR ^1H chemical shifts of the two methyl groups (d and s overlapped, 1.87−1.90 ppm). Using *n*-butyl cuprate, the two methyl groups were placed in the trans position for the *N*-Boc lactam **6c** and cis for the *N*-methyl analogue **5c**. For compound **6c**, the typical NOE effect between the protons of the methyl group at C4 (s, 1.00 ppm) and H3 (m, 2.27−2.35 ppm) was once again obvious. For the analogue **5c**, NOE analysis displayed undoubtedly a relationship between on one hand the two methyl group (s, 0.84 ppm and d, 1.13 ppm for methyl at C4 and C3 respectively) and on another hand H3 (m, 2.14−2.23 ppm) and the methylene protons of the butyl chain (m, 1.20−1.33 ppm), a result consistent with the synperiplanar position of the two methyl groups.



5a,**6a** **6c** **5c**

Figure 2. Noesy correlations of piperidinones **5**−**6a**,**c** outlined with curly arrows.

Due to the conditions used allowing the conformational equilibration and the in situ epimerization on C3, the

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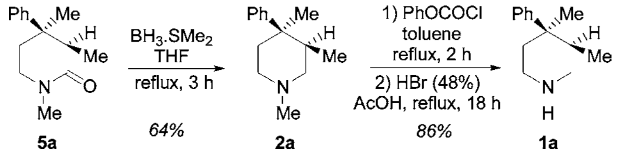
(10) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029.

(11) THF was the best solvent for the 1,4-addition of 4-fluorophenyl cuprate to the 3-methoxycarbonyldihydropiperidinone in the formal synthesis of paroxetine; see ref 8d.

Scheme 2. Synthesis of Piperidine **1a**



stereoisomers obtained seemed to correspond with the thermodynamically stable forms.[8e] We tried to rationalize these results with molecular modeling calculations. The structures of compounds **5a**, **6a**, **5c**, and **6c** as well as those of their 4-epimers were optimized both at the MM[12] and PM3 levels of theory. The substituent at C4 was placed in either pseudoaxial or pseudoequatorial positions, leading to energy differences lower than 1 kcal/mol for piperidinones **5a**,**c** and **6a** and their epimers. Thus, the obtained energies could not illustrate the results described above. However, a significant energy difference (1.14 and 1.79 kcal/mol for the MM and PM3 levels, respectively) was found between the compound **6c** and its epimer in favor of the *trans*-dimethyl isomer **6c** as experimentally observed.

Finally, lactam **5a** was involved in a reduction/deprotection sequence to afford the *trans*-3,4-dimethyl-4-phenylpiperidine **1a** with a 55% overall yield (Scheme 2).

In conclusion, we have described for the first time that 3,4,4-trisubstituted piperidinones **5** and **6a**−**c** could be accessed by the conjugate addition of organocuprate to 3,4-dimethyl-5,6-dihydropyridinones. This reaction was diastereoselective and allowed the development of an efficient synthesis of the *trans*-3,4-dimethyl-4-phenylpiperidine **1a**, an analogue of the key intermediate **A** for the preparation of compounds of biological interest. The scope and limitation of this strategy for the synthesis of 4-arylpiperidines such as piperidine **A** are currently underway.

Acknowledgment. We thank the “Ministére de la Recherche et des Nouvelles Technologies”, CEA (Commissariat á l’Energie Atomique), CNRS (Centre National de la Recherche Scientifique), the “PUNCH-Orga” Network (Pôle Universitaire Normand de Chimie Organique), the “Région Basse-Normandie”, and the European Union (FEDER funding) for financial support. We are grateful to the CRIHAN (Centre de Ressources Informatiques de Haute-Normandie, Rouen) for technical support concerning molecular modeling calculations and Rémi Legay from the Laboratoire de Chimie Moléculaire et Thioorganique (ENSICAEN, Caen) for the NOESY experiments.

Supporting Information Available: Experimental procedures, analytical data for products **1a**, **2a**, **3**, **4**, **5a**−**c**, and **6a**−**c**, and details of molecular modeling calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] Molecular mechanics calculations were performed with the CVFF force field as implemented in the Cerius^2 package. PM3 calculations were done with the VAMP module of the MS Modeling package. Both software packages were supplied by Accelrys, Inc.