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EFFICIENT ROUTE TO THE SYNTHESIS OF C-2, C-3 SUBSTITUTED 4-PIPERIDONES

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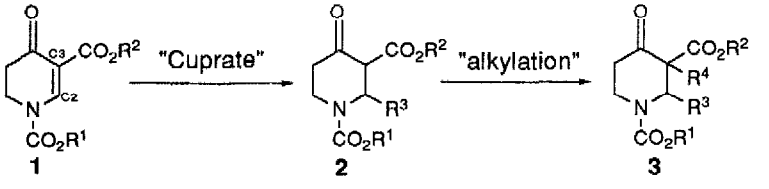
Abstract: 1-Carbobenzoxy-3-carbomethoxy-5,6-dihydro-4-pyridone (**1**) has proven to be exceptionally receptive in the conjugate addition of organocuprates to give C-2 substituted piperidones having the C-3 position activated toward alkylation. Enone **1** was used as the key synthon in the synthesis of C-1, C-2 and C-3 substituted 4-piperidinol (**8**).

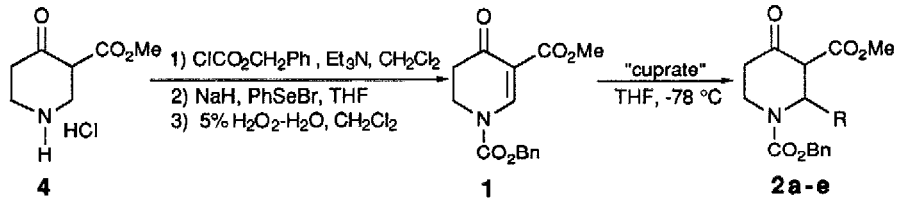
4-Piperidones are valuable synthons for the preparation of alkaloids and pharmaceuticals.[1] While several methods have been developed to efficiently introduce substituents at the C-2 centre of 4-piperidone,[1,2] general procedures for the functionalization of the C-3 centre of C-2 substituted derivatives are limited.[1,2d,e] We required C-2 monosubstituted as well as C-2, C-3 disubstituted 4-piperidones for the synthesis of mimics of the first formed carbocation intermediate in the enzymatic cyclization of 2,3-oxidosqualene to lanosterol.[3] The available methods for the synthesis of these inhibitors were insufficient to this end[4] and we have developed an efficient methodology that allows fuctionalization at C-2 and C-3 of 4-piperidones (Scheme 1).



Scheme 1

Our strategy utilizes enone, **1**, and takes advantage of the reactivity of α, β-unsaturated carbonyl systems to introduce substituents at the β position (C-2 of 4-piperidones) as well as the potential of β–dicarbonyl compounds to undergo alkylation (C-3 position of the 4-piperidone). Vinylogous

amides are known to undergo Cu(I) mediated conjugate addition of Grignard reagents to produce C-2 substituted derivatives.[2a,b,5] Therefore, as expected, organocuprate reagents derived from Grignards and alkyl lithium reagents added to enone, **1**, with great ease and in relatively high yields (Table 1).



4 **1** **2a-e**

Scheme 2

Enone **1**[6] is prepared from commercially available 3-carbomethoxy-4-piperidone hydrochloride (**4**) by initial protection with benzyl chloroformate followed by the introduction of the unsaturation *via* established selenium chemistry[7] (Scheme 2) in overall yield of 70-75%.

Table 1. Conjugate additions to enone **1**.

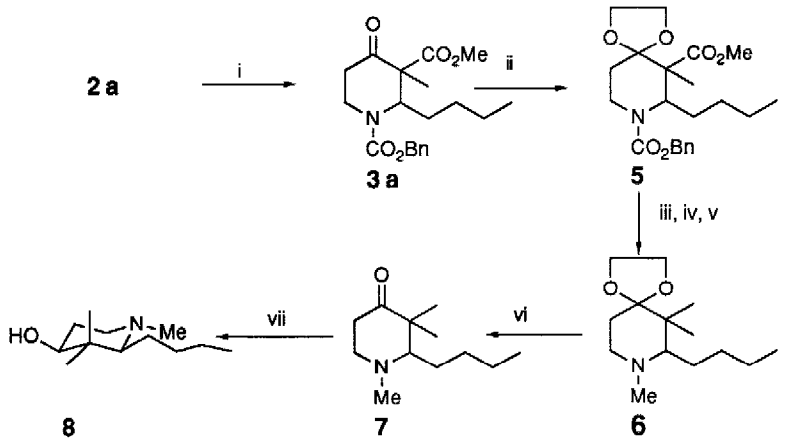
Entry	Cuprate	**2**[a] (R=)		Yield (%)[b]
1	$Bu_2Cu(CN)Li_2$[c]	**a**	Bu	91
2	$(PhCH_2)_2Cu(CN)(MgBr)_2$[c]	**b**	$PhCH_2$	77
3	(TBDMSO)$_2$Cu(CN)(MgBr)$_2$[d]	**c**	TBDMSO	52[f]
4	Cu(2-Th)(CN)Li$_2$[e]	**d**		85[f]
5	Cu(2-Th)(CN)Li$_2$[e]	**e**		90[f]

[a]All compounds were fully characterized by IR, ^1H and ^{13}C NMR, MS, and elemental analysis. [b]Yields are for isolated products. [c]n-BuLi and $PhCH_2MgBr$ were purchased from Aldrich Chemical Company. [d]Grignard was prepared from the corresponding bromide. [e]The lithium species were prepared from the corresponding iodides and 2.2 eq. t-BuLi in Et_2O at -78 °C; 2-Th=2-thienyl. [f]The yields are based on the starting halides.

Cuprate addition reaction to **1** is best carried out in THF or THF/Et_2O mixture at -78 °C. A typical procedure involves the addition of enone **1** in THF to the preformed cuprate reagent at -78 °C. The reaction is instantaneous and can usually be worked up within 30 min. by the addition of sat. NH_4Cl/NH_4OH (pH~8) at -78 °C. Chromatography on silica gel or crystallization allows easy purification of most C-2 substituted products (Table 1).[8]

Yields are limited only by the efficiency in formation of the organometallic species (ie. alkyl lithiums *vs* alkyl Grignards). On a relatively small scale, 0.25 mmol to 2.0 mmol, we found it advantageous to generate the higher order (H.O.) cyanocuprates[9] from alkyl lithium reagents and lithium 2-thienylcyanocuprate.[10] Grignard formation on this scale was troublesome and gave much lower yields (**2c** *vs* **2d** and **2e**) than the alkyl lithium formed by lithium-iodine exchange.[11]

The applicability of this methodology is exemplified in the synthesis of 2-butyl-1,3,3-trimethyl-4-piperidinol **8** (Scheme 3)[12], a possible inhibitor of 2,3-oxidosqualene:lanosterol cyclase. The C-2 substituted β-keto ester[13], **2a**, was first methylated at C-3 to give **3a**. Ketalization of **3a** gave **5**, reduction of which with excess $LiAlH_4$ followed by tosylation and hydride displacement with $LiBEt_3H$ yielded amino-ketal **6**. Hydrolysis of the ketal gave piperidone, **7**, which was then stereoselectively reduced[14] at -78 °C to give the required 4-piperidinol **8** in 94% diastereoselectivity.



Reagents: (i) NaH, DME, 0 °C then MeI, R.T. 40 hr; (ii) $(CH_2OH)_2$, H^+, toluene; (iii) $LiAlH_4$, THF; (iv) n-BuLi, Et_2O, TsCl; (v) $LiBEt_3H$, THF, 50 °C; (vi) 2N HCl, reflux ; (vii) $LiAlH_4$, THF, -78 °C.

Scheme 3

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References and Notes

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3 van Tamelen, E. E.; James, D. R. J. Am. Chem. Soc. **1977**, 99, 950.

4. Most C-2, C-3 disubstituted 4-piperidones required in our study are sensitve to strong acid. Therefore the procedure outlined in ref. 1 could not be used; the procedure in ref. 2d and 2e is limited to the introduction of allylic substituents at the C-3 position.

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6. The N-benzoyl derivative has also been prepared using the conditions given for the N-benzyloxy enone, **1**, this also undergoes conjugate additions in high yields.

7. Reich, H. J.; Renga, J. M.; Reich, I. L. J. Am. Chem. Soc. **1975**, 97, 5434.

8. The low yield in the addition product **2c** is the result of poor Grignard formation from the corresponding bromide, presumably as a result of β-elimination, as judged by GC analysis.

9. Lipshutz, B. H.; Koerner, M.; Parker, D. A. Tetrahedron Lett. **1987**, 28, 945.

10. Lithium 2-thienylcyanocuprate is available from Aldrich Chemical Company.

11. Negishi, E-I.; Swanson, D. R.; Ronsset, C. J. J. Org. Chem. **1990**, 55, 5406. Lithium-iodine exchange is especially useful in the formation of homoallylic lithiums.

12. All new compounds were fully characterized by IR, ^{1}H and ^{13}C NMR, MS, and elemental analysis and/or HRMS.

13. The C-2 subsituted derivatives can be decarboxylated using NaCl/ wet DMSO. Decarboxylation of C-3 alkylated β-keto ester required LiI in collidine.

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