A USEFUL CONSTRUCTION OF 4-SUBSTITUTED 1-ALKYLPIPERID-3-ONES

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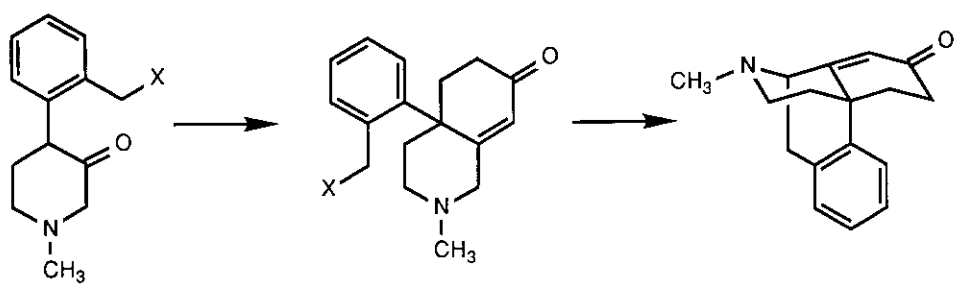
Abstract —— A potentially general construction of 4-substituted 1-alkylpiperid-3-ones is described which employs 3-methoxy-4-bromopyridine as the crucial reagent. This substance is coupled at C-4 with Grignard reagents through the Kumada reaction. The resulting pyridines are then N-alkylated and subsequently subjected to borohydride reduction and aqueous acidic hydrolysis to reveal the title piperidones and related substances.

As part of a program aimed at developing a short, efficient, and enantioselective synthesis of the morphine alkaloids and other morphinans[1] *via* the strategy outlined in Scheme I, we required a route to 1-methylpiperid-3-ones bearing various aryl substituents at C-4. Herein we discuss several attempts to discover such a route and describe a potentially general and useful construction of 4-substituted 1-alkylpiperid-3-ones.

Scheme I

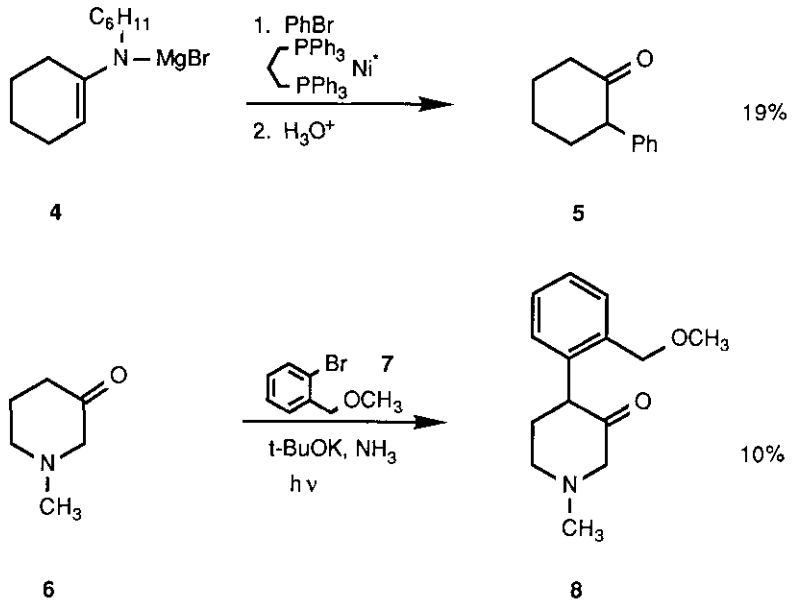


1 **2** **3**

At the outset, we envisioned that arylation of the appropriate enolate or enolate equivalent[2] derived from 1-methylpiperid-3-one[3] would provide straightforward access to the target structures. However repeated attempts to induce the nickel catalyzed phenylation of the halomagnesium salt of cyclohexanone cyclohexylimine (**4**) led only to modest yields of 2-phenylcyclohexanone (**5**) after hydrolytic work-up (Scheme

II). This lack of success on the simplest model system was disappointing in light of the successful nickel catalyzed **allylation** of magnesium enamines[4] and discouraged our examination of **6**. Attempts to involve **6** and **7** in an SRN1 mediated arylation[5] again led to low yields of the desired **8**.

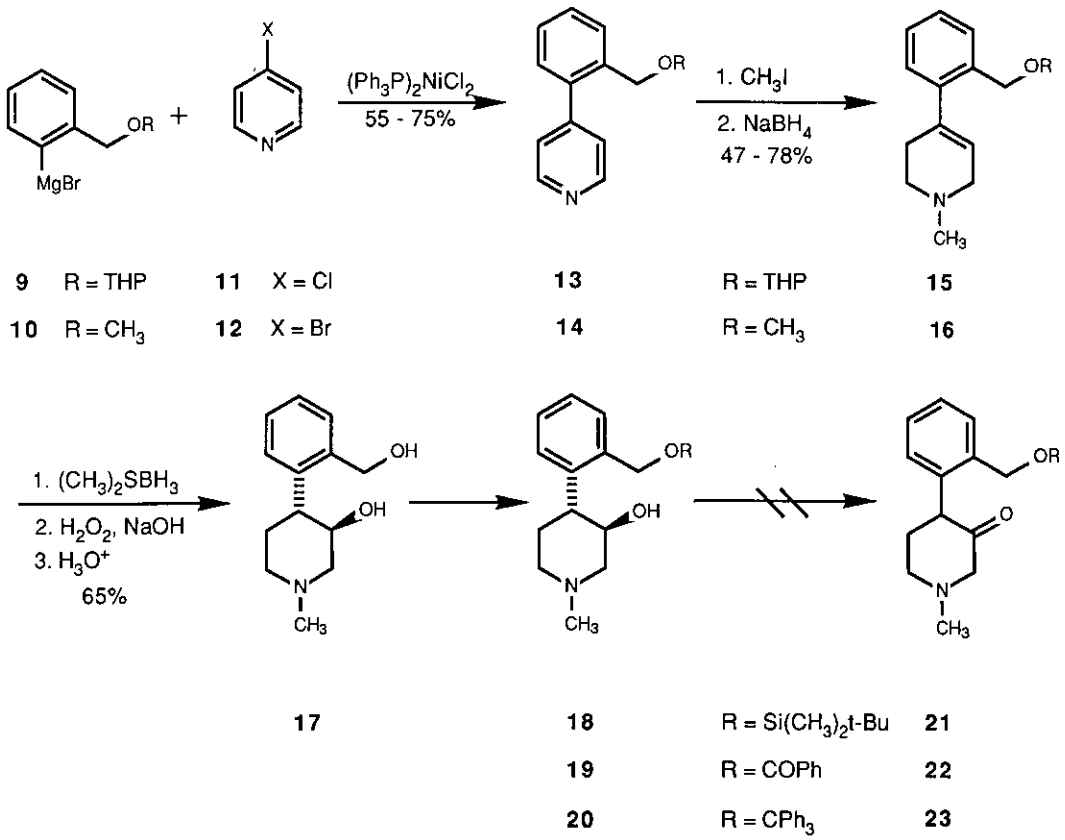
Scheme II



*REDUCED PHOSPHINE-LIGATED NICKEL DIHALIDE

Given the failure of the above two direct approaches to the arylpiperidones of interest, we next investigated a somewhat less direct route wherein the critical carbon-carbon bond between carbocycle and heterocycle would be made at the pyridine oxidation level. This implies the intermediacy of unsymmetrical biaryls, a class of substances now readily available through several organometallic approaches, including the Kumada reaction.[6] The implementation of this approach began with the nickel catalyzed coupling of Grignard reagents **9** and **10** with either 4-chloro- or 4-bromopyridine (**11** and **12**) to yield **13** and **14** (Scheme III). Their transformation into the corresponding N-methyl pyridinium salts and subsequent borohydride reduction led to tetrahydropyridines **15** and **16**, respectively. Hydroboration/oxidation of **15** and **16** and then exposure to aqueous HCl under conditions sufficient to disrupt the resulting amine-borane complexes invariably removed the benzylic hydroxyl protecting groups, providing **17**. Although benzylic oxygen protection could be reinstated at this point to provide **18-20**, their further oxidation to complete the piperidone system proved to be problematic. For example, pyridinium dichromate (PDC) and sodium acetate buffered pyridinium chlorochromate (PCC) appeared to destroy the piperidine nuclei while Swern oxidation of **20** consistently left it unscathed.

Scheme III



9	R = THP	**11**	X = Cl	**13**	R = THP **15**
10	$R = CH_3$	**12**	X = Br	**14**	$R = CH_3$ **16**

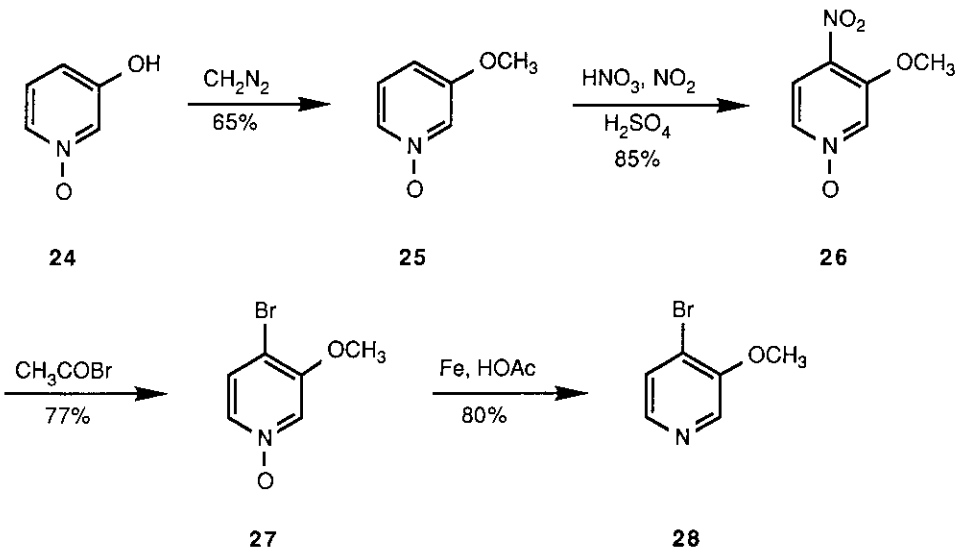
17

18	$R = Si(CH_3)_2t\text{-}Bu$	**21**
19	R = COPh	**22**
20	$R = CPh_3$	**23**

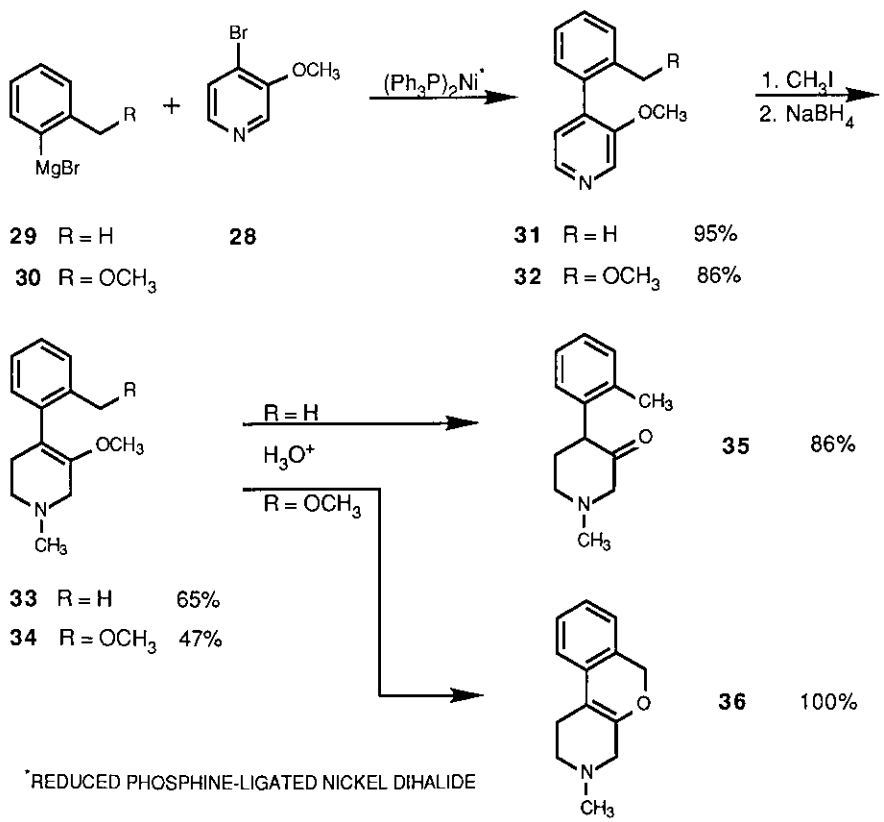
Since the only significant shortcoming of the above approach to the required arylpiperidones was the unanticipated difficulty in modifying C-3 oxidation state, we decided to provide the C-3 oxygen at the halopyridine stage, thereby revealing a masked C-3 carbonyl upon reaching the tetrahydropyridine intermediate. To put this scheme into practice, we required a 3-alkoxy-4-halopyridine to involve in the initial Kumada reaction. Through chemistry adapted largely from den Hertog,[7] 3-methoxy-4-bromopyridine **28** proved to be available from commercial material in four simple steps (Scheme IV). Its coupling with Grignard reagents **29** and **30** proceeded without incident to yield biaryls **31** and **32**, respectively, whose N-methylation and borohydride reduction provided corresponding tetrahydropyridines **33** and **34** (Scheme V). Their hydrolysis led to **35** in the case of **33** and to internal enol ether **36** in the case of **34**, thus culminating our approach to the appropriately substituted piperid-3-ones and their related enol ethers.

As the scope of the Kumada reaction is known to be broad, encompassing the coupling of both alkyl and aryl substituents and being reasonably tolerant of steric hinderance, and since we have demonstrated herein that the 4-substituted 3-methoxypyridines derived through Kumada reactions on 3-methoxy-4-bromopyridine (**28**)

Scheme IV



Scheme V



can be efficiently converted to 1,4-disubstituted piperid-3-ones, we suggest that **28** can function as a useful reagent for the general preparation of such heterocyclic systems.

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