Synthesis of C-Substituted Cyclic Amines Using Azacycloalkyl Organozinc Reagents

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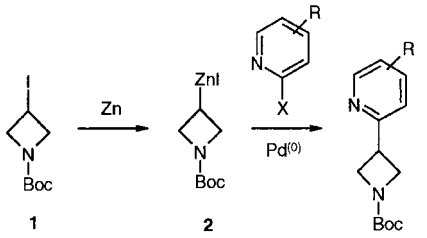
Abstract: Azetidine and piperidine derived organozinc species have been prepared from the corresponding azacycloalkyl iodides by direct Zn insertion. They have been shown to readily undergo $Pd^{(0)}$ mediated cross-coupling reactions and to transmetallate with CuCN.2LiCl.

During the course of our studies towards new agents for the treatment of asthma we became interested in preparing 3-(2-pyridyl) azetidines[1].

3-Aryl azetidines are generally synthesised by reduction of 3-aryl azetidine-2-ones[2] or base-mediated ring closure of the appropriate N-O-ditosyl-2-aryl-3-amino-propan-1-ols[3]. However, both routes rely on non-readily accessible 2-aryl-2-cyanoacetates and require the use of reagents which might not be suitable for substrates containing sensitive functionalities.

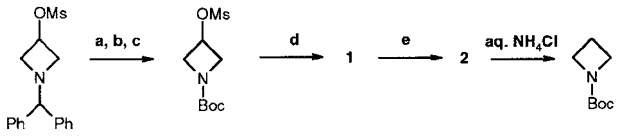
Due to their high functional group tolerance, organozinc reagents are attractive intermediates in C-C bond formation reactions[4], and we chose to investigate the convergent synthesis of 3-(2-pyridyl) azetidines by the $Pd^{(0)}$-mediated cross-coupling of an azetidinyl zincate reagent with a 2-halopyridine. Previously Knochel[5] had shown that Zn insertion into the C-I bond of an acyclic ß-iodocarbamate was possible, although it was not clear at the outset of our work whether a similar reaction could be performed with cyclic substrates. Consequently, we targeted the synthesis of the Boc-protected iodo-azetidine **1** and examined its metallation with Zn. We felt that, if successful, this approach would also allow access to a variety of 3-aryl azetidines (Scheme 1).



Scheme 1

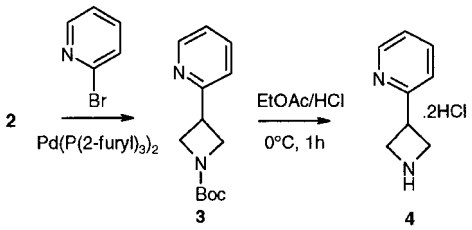
The synthesis of **1** was achieved starting with N-benzhydrylazetidinyl-3 mesylate[6] (Scheme 2). Removal of the benzhydryl group with α-chloroethyl chloroformate (ACE-Cl) followed by Boc-protection afforded N-Boc-azetidinyl-3 mesylate which reacted with KI in DMSO at elevated temperature to give **1** in good yield. We were then pleased to find that Zn insertion into the C-I bond of **1** could be achieved following the procedure described by Knochel[7]. Formation of the organozinc species **2** was followed by TLC and was complete after 45 min. at room temperature. This was confirmed by quenching the reaction mixture with aqueous NH_4Cl followed by ^1H NMR analysis of the crude organic phase showing N-Boc-azetidine as the main product. To our knowledge, Zn insertion into azacycloakyl iodides is unprecedented. Having established that we could easily prepare the organozinc reagent **2**, our attention was then directed to demonstrating that it could undergo $Pd^{(0)}$ mediated cross-coupling reactions.

Thus, 2-bromopyridine was added to a freshly prepared solution of **2** in THF and the mixture was heated at 65°C in the presence of $Pd_2(dba)_3$ and $P(2\text{-furyl})_3$[8] for 2 h. Using this procedure N-Boc-3-(2-pyridyl)azetidine **3** was isolated in 63% yield after chromatography.



Scheme 2. a) ACE-Cl, 1,2-Dichloroethane, 70°C, 1 h. b) MeOH, reflux, 1 h, 75% over 2 steps. c) $(Boc)_2O$, Et_3N, CH_2Cl_2, rt, 95%. d) KI, DMSO, 140°C, 75%. e) activated Zn, THF, rt, 0.75 h

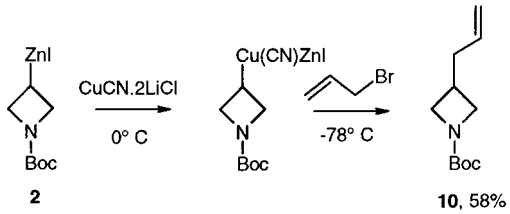
Removal of the Boc protecting group from **3** under standard acidic conditions gave 3-(2-pyridyl) azetidine dihydrochloride **4** in quantitative yield (Scheme 3) .



Scheme 3

Using this methodology we were then able to synthesise various 3-aryl-N-Boc-azetidines[9] and the results are summarized in Table 1. As expected **2** showed wide functional group compatibility. For example, no reaction on a nitrile group was observed (entry 3), and no attack on the carbonyl group of ketone **9** was noticeable (entry 6). The low yield for this acylation reaction might be explained by Zn promoted competitive cleavage of the solvent (THF) by the acid chloride[10]. Moreover, halopyridines showed greater reactivity towards **2** than aryl iodides (entry 1 vs entry 2), although better yields were obtained with aryl iodides bearing an electron-withdrawing group (entry 3 vs entry 2).

The synthetic versatility of the organozinc reagent **2** was further demonstrated by transmetallation with CuCN•2LiCl in THF[7] generating a zinc-copper reagent which was trapped with allyl bromide to give **10** in moderate yield (Scheme 4).

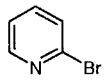
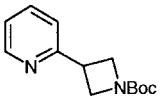
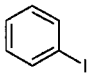
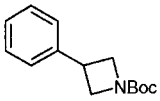
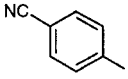
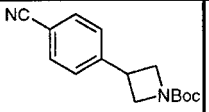
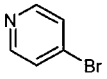
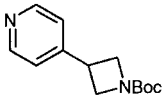
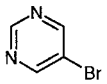
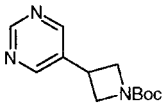
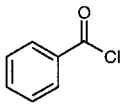
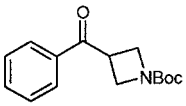


Scheme 4

Having shown that it is possible to access 3-substituted azetidines using the organozinc reagent **2**, we became interested in applying this methodology to piperidines.

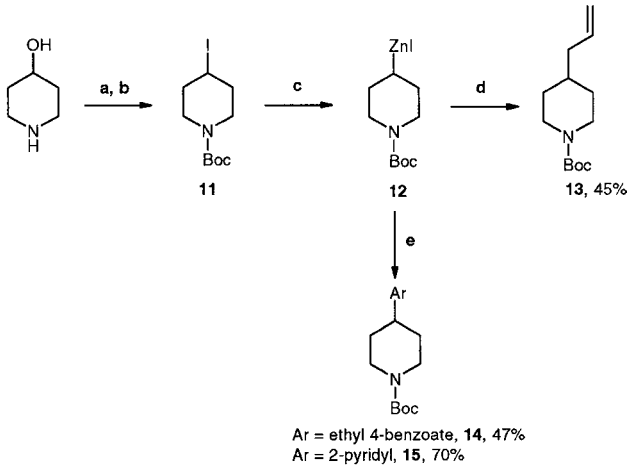
Thus, 4-iodo-N-Boc-piperidine **11** was synthesised in two steps from 4-piperidinol and converted to the organozinc species **12** using similar conditions to those used to generate **2**. As before, formation of **12** could

Table 1

entry	Aryl Halide	Product	Yield
1			**3**, 63%
2			**5**, 47%
3			**6**, 60%
4			**7**, 55%*
5			**8**, 46%
6			**9**, 38%*

** : reaction carried out at room temperature*

be monitored by TLC and ^{1}H NMR. The organozinc reagent **12** was then found to exhibit a similar pattern of reactivity to the azetidine analogue **2**. Thus, reaction of **12** with ethyl 4-iodobenzoate and 2-bromopyridine under $Pd^{(0)}$ catalysis gave rise to the corresponding 4-aryl piperidines in 47% and 70% respectively. **12** could also be allylated after transmetallation with CuCN•2LiCl (Scheme 5).



Scheme 5. a) $(Boc)_2O$, Et_3N, CH_2Cl_2, 0°, 1 h, 96%. b) I_2, PPh_3, Imidazole, CH_3CN, rt, 48 h, 80%. c) activated Zn, THF, 40°C, 2 h. d) CuCN.2LiCl, THF, 5°C, 15 min then allyl bromide, -78°C to rt, 2 h. e) Ar-X, $Pd_2(dba)_3$, P(2-furyl)$_3$, DMA:THF 1:1, 80°C, 2 h

In summary, we have developed a general and practical method for preparing C-substituted 3-azetidines and 4-piperidines *via* the corresponding organozinc reagents, and we envisage that this methodology should be applicable to a wider range of heterocycles.

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References and notes

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9. **Typical procedure:** Zn dust (425 mgs, 6.5 mmoles) was stirred in THF (1ml) under nitrogen and 1,2-dibromoethane (50 µls, 0.58 mmole) was added at room temperature. The mixture was heated at 65°C for 3 min and allowed to cool to room temperature while stirring. Trimethylsilyl chloride (70 µls, 0.55 mmole) was then added and the mixture stirred at rt for 0.5 h. A solution of 3-iodo-N-Boc-azetidine **1** (1.4 g, 5 mmoles) in THF (2.5 mls) was then slowly added (gentle exotherm) and the reaction mixture allowed to stir at room temperature for 45 min. $Pd_2(dba)_3$ (45 mgs, 50 µmoles) and P(2-furyl)$_3$ (46 mgs, 0.2 mmole) were mixed in THF (1ml), the solution stirred at room temperature under nitrogen for 10 min and added to the organozinc reagent solution, followed by iodobenzene (670 µls, 6 mmoles) in THF (10 mls). The mixture was then heated at 65°C for 2 h, cooled, filtered over celite and the filtrate diluted with EtOAc. The filtrate was washed with saturated aqueous $NaHCO_3$ (x2), brine, dried (Na_2SO_4), filtered and evaporated to yellow oil. Flash chromatography of this oil on SiO_2 (19:1 Hexane:EtOAc) afforded 3-phenyl-N-Boc azetidine **5** as a colorless oil (540 mgs, 47%).
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