A New Synthesis of 3-Substituted Pyrrolidines Using Iron Catalysed Cross-coupling Reactions and Ring Closing Metathesis

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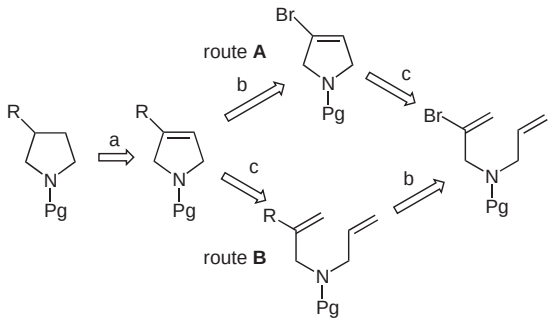
Received 12 August 2002

Abstract: A series of 3-substituted *N*-Boc protected pyrrolidines have been prepared via iron catalysed cross-coupling between Boc protected *N*-allyl-*N*-(2-bromoallyl)amine **3** and organomagnesium compounds followed by ring closing metathesis and subsequent hydrogenation of the formed pyrrolines.

Key words: pyrrolidines, ring closing metathesis, Grignard reagents, iron catalysed cross-coupling

Pyrrolidine is a frequently found motif in numerous naturally occurring alkaloids and biologically active substances.[2,3] Their synthesis has attracted much attention and a wide range of different approaches have been reported which include both inter- and intramolecular reactions.[4]

As a part of a drug discovery program directed towards the synthesis of compounds with muscarinic agonist properties, we became interested in the preparation of 3-substituted pyrrolidines. Ring closing olefin metathesis (RCM)[5,6] is a powerful tool for the construction of functionalised heterocycles. Recently, RCM has been employed for the construction of the 3-pyrrolidine ring in the synthesis of an analogue of swainsonine.[7] This result has prompted us to report our results on the preparation of a series of 3-alkyl and 3-aryl substituted *N*-Boc protected pyrrolidines **8**–**12** from **3** using a combination of iron catalysed cross-coupling, RCM and hydrogenation of the intermediate pyrrolines.



Scheme 1 Retrosyntetic approaches **A** and **B**: a) reduction, b) cross-coupling reaction and c) ring closing metathesis.

We envisaged that the intermediate 3-substituted 3-pyrrolines could be prepared from N-protected *N*-allyl-*N*-(2-bromoallyl)amine via two approaches. **A**: Functionalisation (cross-coupling) of a 3-bromo pyrroline prepared via RCM of the *N*-allyl-*N*-(2-bromoallyl)amine; **B**: RCM of 2-substituted diallylamines prepared via cross-coupling between the *N*-allyl-*N*-(2-bromoallyl)amine and an organometallic reagent (Scheme 1).

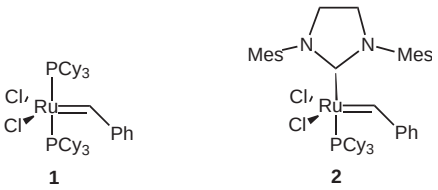


Figure 1

Vinyl bromide **3**[8] did not undergo RCM using Grubb's catalysts **1** or the more active ruthenium catalyst **2** (Figure 1). In addition, Lee et al. have reported that Pd catalysed reactions between 3-trifluorosulfonate-3-pyrroline and arylboronic acids afford 3-arylpyrroles by a tandem Suzuki-dehydrogenation reaction.[9] We therefore decided to investigate route **B** where **3** was functionalised via a transition metal catalysed C–C bond forming reaction prior to RCM. We noted that treatment of N-protected *N*-allyl-*N*-(2-bromoallyl)amines with either catalytic amount of palladium or stoichiometric amount of nickel invariantly gave rise to intramolecular cyclisation.[10,11] Moreover, use of the readily removeable Boc protection group was reported to give complex mixtures, when **3** was treated with an arylboronic acid and a palladium catalyst.[11]

Iron catalysed alkenylation of Grignard reagents was first described by Kochi et al.[12] and later optimised by Cahiez.[13] Cheap and stable iron salts have proved efficient and practicable catalysts for both alkenyl-alkyl cross-couplings and for the coupling of electron-deficient aryl chlorides with alkyl Grignard reagents.[14]

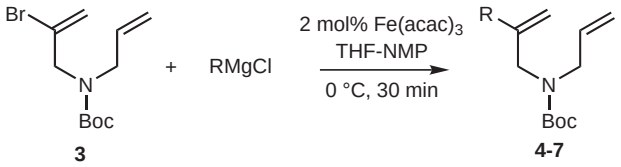
Using this approach, treatment of **3** with 1.5 equivalents of *n*-BuMgCl in THF–NMP at 0 °C for 30 minutes in the presence of 2 mol% $Fe(acac)_3$ resulted in full conversion of **3** and the cross coupled product **4** could be isolated in 64% yield (Table 1). Similarly *i*-PrMgCl and PhMgCl could also be coupled with **3**, however in the latter case

Synlett 2002, No. 11, Print: 29 10 2002.
Art Id.1437-2096,E;2002,0,11,1889,1891,ftx,en;G22602ST.pdf.

ISSN 0936-5214

large amounts of the homocoupling product (biphenyl) was observed. Addition of large excess of PhMgCl (3 equiv) increased the yield of **6** from 37% to 61%. Sterically congested *t*-BuMgCl gave no reaction even if used in large excess (Table 1). As the crude products were generally fairly pure they were used directly in the following step in order to circumvent chromatographic purification. Thus, the crude pyrrolines were ring closed using 10 mol% of **1** or 5 mol% of **2**.

Table 1 Iron Catalysed Cross-coupling of **3** with Grignard Reagents

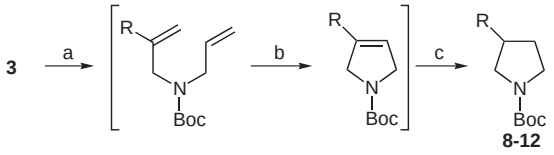


R	Product	Yield (%)
n-Bu	**4**	64
i-Pr	**5**	59[a]
Ph	**6**	37[a] (61)[b]
t-Bu	**7**	0

[a] 2 Equiv of Grignard reagent was used.
[b] 3 Equiv of PhMgCl was used.

This furnished the 3-substituted 3-pyrrolines, which in order to avoid oxidation to the corresponding pyrroles upon exposure to air were reduced to the stable and desired 3-substituted pyrrolidines using hydrogen (3 bar) and Pd/C. Following the procedure described in the reference[15] a range of 3-substituted pyrrolidines were synthesised in 38–55% overall yield in 3 steps from **3** involving only a single and final chromatographic purification (Table 2).

Table 2 Synthesis of Pyrrolidines **8**–**12** from **3**



Entry	R	Product	Yield[d]
1	*n*-Bu	**8**	51%
2	*n*-Pentyl	**9**	55%
3	*n*-Hexyl	**10**	53%
4	*i*-Pr	**11**	52%
5	Ph	**12**	38%[e]

[a] 2 Equiv RMgCl, 1 mol% $Fe(acac)_3$, THF–NMP, 0 °C, 1 h.
[b] 10 mol% of **1** for 36 h or 5 mol% of **2** for 24 h in CH_2Cl_2 at r.t.
[c] 10 mol% Pd/C, 3 atm H_2, MeOH, 24 h.
[d] Yields are isolated overall yields from **3**.
[e] 3 Equivalents of PhMgCl was used.

In summary, a new simple, practical and convenient approach for the synthesis of 3-substituted pyrrolidines starting from **3** has been developed using iron catalysed cross-coupling, ruthenium catalysed ring closing metathesis and palladium catalysed hydrogenation. We are currently investigating the application of this methodology in combination with asymmetric hydrogenation and dihydroxylation for preparation of chiral functionalised pyrrolidines.

Acknowledgement

This work was supported by ACADIA Pharmaceuticals A/S and The Danish Academy of Technical Sciences. The GC-MS was a gift from the Velux Foundation of 1981 and the Ib Henriksen Foundation. The 300 MHz NMR instrument was provided by The Danish National Science Research Council. We are also grateful to Ms. Malene Mohr, LEO Pharma, Denmark, for providing the HRMS data.

References

(1) Current address: Novo Nordisk A/S, Medicinal Chemistry Research, 2760 Måløv, Denmark.
(2) Derwick, P. M. *Medicinal Natural Products*, Chap. 6; J. Wiley and Sons: Chichester, **1997**, 270.
(3) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265.
(4) For general information see: Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862; (contemporary review) and former reviews cited therein.
(5) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
(6) Fürstner A.; *Angew. Chem. Int. Ed.;* **2000**, *39*: 3012.
(7) Lindsay, K. B.; Tang, M.; Pyne, S. G. *Synlett* **2002**, 731; for the application of RCM reaction to the synthesis of pyrrolines see references cited therein.
(8) Compound **3** was synthesized in ~20 g scale from allylamine and 2,3-dibromopropene followed by Boc protection using the procedure described by: Shi, L.; Narula, C. K.; Mak, K. T.; Kao, L.; Xu, Y.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 3894.
(9) Lee, C.-W.; Chung, Y. J. *Tetrahedron Lett.* **2000**, *41*, 3423.
(10) Cancho, Y.; Martin, J. M.; Martinez, M.; Llebaria, A.; Moreto, J. M.; Delgado, A. *Tetrahedron* **1998**, *54*, 1221.
(11) Lee, C.; Oh, K. S.; Kim, K. S.; Ahn, K. H. *Org. Lett.* **2000**, *2*, 1213.
(12) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487.
(13) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199.
(14) Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 609.
(15) **Typical Procedure**: To a stirred solution of allyl-(2-bromoallyl)-carbamic acid *tert*-butyl ester (**3**) (1.49 g, 5.4 mmol) and $Fe(acac)_3$ (38 mg, 2 mol%) in THF (7.5 mL) and NMP (5.4 mL) at 0 °C was added a THF solution of *i*-PrMgCl (6.0 mL, 1.8 M, 10.8 mmol) drop wise over a period of 30 min. After stirring for 1 h the reaction mixture was quenched with sat. NH_4Cl (20 mL) followed by extraction with CH_2Cl_2 (3 × 20 mL). Drying of the organic layers (Na_2SO_4) and removal of the solvents in vacuo gave crude **5**. An analytically sample was purified on silica gel (heptane/EtOAc 20:1). Data for **5**: ^{1}H NMR: δ = 5.84–5.68 (m, 1 H), 5.16–5.03 (m, 2 H), 4.86 (br s, 1 H), 4.73 (br s, 1 H), 3.88–3.68 (m, 4 H), 2.26–2.14 (m, 1 H), 1.46 (s, 9 H), 1.06 (d, *J* = 7 Hz, 6 H). ^{13}C NMR: δ = 151.0 (s), 144.4 (s), 133.9 (d), 116.5 and 116.2 (t), 108.0 and 107.5 (t), 49.4 and 48.3 (t),

31.2 (d), 28.4 (q), 21.7 (q). HRMS calcd for $C_{14}H_{25}NO_2$: 239.1886. Found: 239.1877. The crude residue was dissolved in degassed CH_2Cl_2 (270 mL) and **2** (229 mg, 5 mol%) were added. After stirring for 24 h at r.t. under nitrogen the solvent was removed in vacuo. The mixture was redissolved in MeOH (20 mL) and 10 wt% Pd/C (400 mg) was added. The mixture was stirred in a hydrogen atmosphere (3 bar) for 24 h and then filtered through celite and gently concentrated in vacuo. Purification on silica gel (heptane/EtOAc 20:1) provided 630 mg (52%) of **11** as a clear oil. Data for **11**: ^{1}H NMR: δ = 3.59–3.44 (m, 2 H), 3.26–3.15 (m, 1 H), 2.91–2.82 (m, 1 H), 2.03–1.92 (m, 1 H), 1.87–1.71 (m, 1 H), 1.54–1.35 (m, 11 H), 0.96–0.89 (m, 6 H). ^{13}C NMR: δ = 154.7, 78.7, 50.1, 46.1, 45.9, 31.8, 29.9, 28.3, 21.2, 20.9. HRMS calcd for $C_{12}H_{23}NO_2$: 213.1729. Found: 213.1724.