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An efficient one-pot synthesis of annulated pyridines utilising a directed *ortho*-metallation/transmetallation approach

Antony J. Davies,* Karel M. J. Brands, Cameron J. Cowden, Ulf-H. Dolling and David R. Lieberman

Department of Process Research, Merck Sharp & Dohme Research Laboratories, Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK
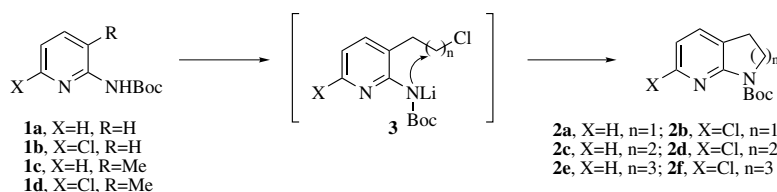
Abstract—The *ortho*-alkylation of Boc-protected aminopyridines with α,ω-dihaloalkanes followed by *in situ* cyclisation, resulted in the corresponding annulated pyridine derivatives in good to excellent yields. The effect of the alkylating and chelating agents, the transmetallation additives and the directing group was examined.
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Substituted pyridines and their annulated derivatives represent an important class of organic compounds, being fully represented in a plethora of natural products[1] and pharmaceutical applications.[2] As part of an ongoing research effort aimed at the preparation of $\alpha_v\beta_3$ integrin antagonists,[3] we recently required an efficient and robust synthesis of compounds with the general structure **2**. Various methods for the preparation of 2,3-dihydro-*1H*-pyrrolo[2,3-*b*]pyridines,[4] 1,2,3,4-tetrahydro-1,8-naphthyridines[5] and 2,3,4,5-tetrahydro-*1H*-pyrido[2,3-*b*]azepines[6] have been reported in the literature. Unfortunately, most of these methods require several steps and are inefficient. Obviously, a universal synthetic method, which allows entry into these annulated systems would be highly desirable. We envisaged a general strategy based on the directed *ortho*-metallation (DoM) of compounds of type **1**. Alkylation of deprotonated **1** with α,ω-dihaloalkanes followed by *in situ* cyclisation should furnish the desired bicyclic product **2** (Scheme 1). The organic literature is replete with examples of the DoM reaction on aromatic substrates.[7] The methodology has been less well utilised in π-deficient heteroaromatics, however, mainly due to side reactions involving nucleophilic addition of the alkyllithium reagent to the azomethine bond of the azine. Reed et al. have reported a DoM approach, which provided 1,2,3,4-tetrahydro-1,6-naphthyridines in low yield. The approach reportedly failed, however, when applied to the preparation of the 1,2,3,4-tetrahydro-1,8-naphthyridine **2c**, giving 'a number of unidentified products'.[8]
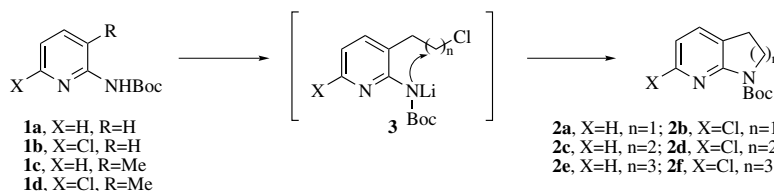

1a, X=H, R=H
1b, X=Cl, R=H
1c, X=H, R=Me
1d, X=Cl, R=Me

2a, X=H, n=1; **2b**, X=Cl, n=1
2c, X=H, n=2; **2d**, X=Cl, n=2
2e, X=H, n=3; **2f**, X=Cl, n=3

Scheme 1.

* Corresponding author. Tel.: +44-1992-452012; fax: +44-1992-452581; e-mail: tony_davies2@merck.com

Table 1.

1a, X=H, R=H
1b, X=Cl, R=H
1c, X=H, R=Me
1d, X=Cl, R=Me

2a, X=H, n=1; **2b**, X=Cl, n=1
2c, X=H, n=2; **2d**, X=Cl, n=2
2e, X=H, n=3; **2f**, X=Cl, n=3

Substrate **1**	R–Li	Additive	Copper(I) halide	Electrophile	Product **2**	Yield%[a]
1a	*s*-BuLi	TMEDA	—	Cl(CH$_2$)$_2$I	**2a**	0
1a	*s*-BuLi	TMEDA	—	Cl(CH$_2$)$_3$I	**2c**	54
1a	*s*-BuLi	TMEDA	—	Cl(CH$_2$)$_4$I	**2e**	55
1d	*n*-BuLi	—	—	Cl(CH$_2$)$_2$I	**2d**	0
1c	*n*-BuLi	—	—	Cl(CH$_2$)$_3$I	**2e**	86
1c	*n*-BuLi	—	—	Cl(CH$_2$)$_2$Br	**2c**	0
1b	*n*-BuLi	TMEDA	—	Cl(CH$_2$)$_4$Br	**2f**	51
1b	*n*-BuLi	TMEDA	—	Cl(CH$_2$)$_3$I	**2d**	51
1b	*n*-BuLi	TMEDA	—	Cl(CH$_2$)$_4$I	**2f**	85
1b	*n*-BuLi	TMEDA	—	MeI	**1d**	91
1b	*n*-BuLi	TMEDA	CuCl	Cl(CH$_2$)$_3$I	**2d**	95
1b	*n*-BuLi	TMEDA	CuBr	Cl(CH$_2$)$_3$I	**2d**	94
1b	*n*-BuLi	TMEDA	CuBr·Me$_2$S	Cl(CH$_2$)$_3$I	**2d**	94
1b	*n*-BuLi	TMEDA	CuI	Cl(CH$_2$)$_3$I	**2d**	98
1b	*n*-BuLi	TMEDA	CuBr·Me$_2$S	Cl(CH$_2$)$_4$I	**2f**	90 (86)
1b	*n*-BuLi	TMEDA	CuBr	Cl(CH$_2$)$_2$I	**2b**	57
1b	*n*-BuLi	TMEDA	CuBr·Me$_2$S	Cl(CH$_2$)$_2$I	**2b**	52
1a	*n*-BuLi	TMEDA	CuBr·Me$_2$S	Cl(CH$_2$)$_2$I	**2a**	45

[a] Yield refers to HPLC assay yield, obtained by comparison with an isolated pure standard. Yield in parenthesis refers to isolated yield, obtained by silica gel chromatography.

In this paper we disclose two complementary DoM methodologies for the construction of annulated pyridines **2** starting from the readily available Boc-protected aminopyridines **1a–b** or aminopicolines **1c–d**.[9] Previously in these laboratories, we have utilised DoM methodology for the construction of the 7-az-aindole nucleus starting from picoline derivative **1c**.[10] Indeed, selective lateral metallation of **1c** can be achieved with 2.2 equiv of *n*-BuLi at 0 °C in high yield without the use of an additive such as TMEDA. The dianion, thus formed, can be quenched with simple electrophiles (MeI, DMF) in close to quantitative yields. We were gratified to find that quenching the resulting dianion at −78 °C[11] with 1-chloro-3-iodopropane resulted in complete (>99:1) conversion to the corresponding chlorobutyl intermediate **3**. Warming the reaction mixture to reflux effected clean ring closure to give the pyrido[2,3-*b*]azepine **2e** in 86% overall yield.[12]

Attempts to extend the reaction to the preparation of 3,4-dihydro-1,8-naphthyridine **2c** starting from **1c** and 1-chloro-2-bromoethane were thwarted by lithium/bromine exchange, which led to subsequent alkylation by the remaining benzyl anion to give dimer **5** in 63% yield. The fleeting presence of **4** could be demonstrated via a cold hydrolytic quench and LCMS analysis. In the case of the related **1d**, we were unable to control the selectivity of the alkylation. A complex mixture ensued, in which the major product was identified as dimer **6** by LCMS.

4

5

6
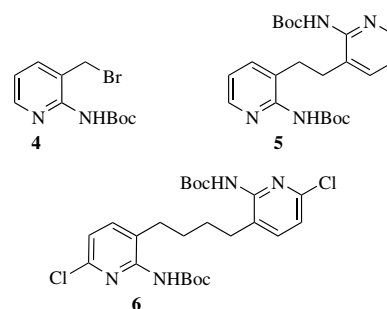
The latter two results led us to explore an approach using Boc-aminopyridines **1a–b**. The 3-H proton in **1a–b** is less acidic than the methyl protons in **1c–d**. High yielding lithiation could be achieved with a slight excess (2.2 equiv) of an equimolar TMEDA/*n*-BuLi solution for the more acidic **1b**,[13] whilst **1a** required more forcing conditions (TMEDA/*n*-BuLi at −10 °C or TMEDA/*s*-BuLi at −78 °C). We found it beneficial in terms of conversion to age the TMEDA/BuLi mixtures for ~30 min at −20 °C *prior* to the addition of substrate **1**. Other potential chelating agents (**A–E**) and bases (LDA, LiHMDS, *i*-PrMgCl) were screened, however, none were as effective as the BuLi/TMEDA combination.[14]

The lithiation of **1b** was cleaner than that of the unsubstituted compound **1a**, due to competing nucleo-

A   B   C

D   E
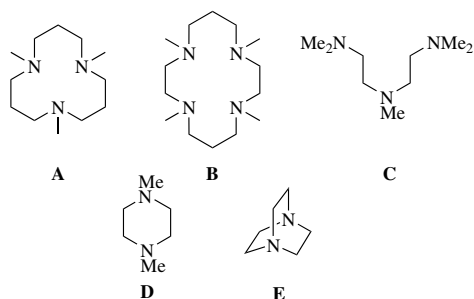
philic addition of *n*- or *s*-BuLi to give the corresponding dihydropyridine derivative. We were delighted to find that alkylation of dilithiated **1b** with 1-chloro-4-iodobutane was facile (90–95% conversion to **3**). Subsequent *in situ* ring closure yielded the pyrido[2,3-*b*]azepine **2f** in 85% overall yield.

Surprisingly, when this reaction was performed with 1-chloro-3-iodopropane, the conversion to intermediate **3** was poor with approximately equal amounts of protonation and alkylation. As expected, ring closure of the *N*-lithio species was more facile for the six-membered ring, occurring in the 0–25 °C range and **2d** was isolated in 51% yield. We believe that the difference in performance between 1-chloro-3-iodopropane and its methylene homologue, might have been due to the higher acidity of the protons β to iodine in the former. Since dilithiated **1b** was also thought to be more basic than dilithiated **1c**, we decided to attenuate the dianion's basicity by transmetallation. Indeed, transmetallation with any copper(I) halide (CuCl, CuBr, CuBr·Me₂S and CuI proved to be equally effective) followed by the addition of the α,ω-dihalide, resulted in excellent conversion of **1b** (>99:1).[15] Similar results were seen in the unsubstituted series (70–80% conversion of **1a**). Subsequent *in situ* cyclisation gave the desired annulated pyridines **2** in good to excellent yields (Table 1).

In conclusion, we have demonstrated a facile and general one-pot preparation of perhydro-*1H*-pyrido[2,3-*b*]azacycloalkanes starting from either *N*-Boc aminopicolines or pyridines. We have established that in selected cases, transmetallation with Cu(I) halides can overcome difficulties, which have previously been observed in this area.[8] Critically, the process performs exceptionally well with a 6-chloro substituent in the starting material, thus providing products, which can be further functionalised via various coupling methods (Suzuki, Sonogashira, Heck etc.).

References and notes

1. Pertinent reviews: (a) Plunkett, O.; Sainsbury, M. In *Rodd's Chem. Carbon Compd.*, 2nd ed.; 1998; Vol. *4(Part F/Part G(partial))*, p 365; (b) Bailey, T. D.; Goe, G. L.; Scriven, E. F. V. *Chem. Heterocycl. Compd.* **1984**, *14* (Pyridine Its Deriv., Pt. 5), 1; (c) Thummel, R. P. *Chem. Heterocycl. Compd.* **1984**, *14* (Pyridine Its Deriv., Pt. 5), 253; (d) Kumar, R.; Chandra, R. *Adv. Heterocycl. Chem.* **2001**, *78*, 269.

2. (a) Selected articles: Ghisalberti, E. L. *Phytomedicine* **1998**, *5*, 147; (b) Pinder, A. R. *Methods Plant Biochem.* **1993**, *8* (Alkaloids and Sulphur Compounds), 241; (c) Bernofsky, C. *Coenzymes Cofactors* **1987**, *2* (Pyridine Nucleotide Coenzymes, Pt. B), 105; (d) Altomare, C.; Summo, L.; Cellamare, S.; Varlamov, A. V.; Voskressensky, L. G.; Borisova, T. N.; Carotti, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 581; (e) Da Settimo, F.; Marini, A. M.; La Motta, C.; Simorini, F.; Luchetti, E.; Bertini, S. *Farmaco* **1996**, *51*, 725.

3. Meissner, R. S.; Perkins, J. J.; Duong, L. T.; Hartman, G. D.; Hoffman, W. F.; Huff, J. R.; Ihle, N. C.; Leu, C.-T.; Nagy, R. M.; Naylor-Olsen, A.; Rodan, G. A.; Rodan, S. B.; Whitman, D. B.; Wesolowski, G. A.; Duggan, M. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 25.

4. Taylor, E. C.; Macor, J. E.; Pont, J. L. *Tetrahedron* **1987**, *43*, 5145.

5. (a) Keller, P. C.; Marks, R. L.; Rund, J. V. *Polyhedron* **1983**, *2*, 595; (b) Hawes, E. M.; Davis, H. L. *J. Heterocycl. Chem.* **1973**, *10*, 39; (c) Armarego, W. L. F. *J. Chem. Soc. C* **1967**, *5*, 377; (d) Trecourt, F.; Marsais, F.; Gungor, T.; Quéguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, *9*, 2409.

6. Jossang-Yanagida, A.; Gansser, C. *J. Heterocycl. Chem.* **1978**, *15*, 249.

7. For general reviews on the directed *ortho*-metallation reaction, see: (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1; (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879; (c) For more focussed reviews on the metallation of azines and diazines, see: Mongin, F.; Quéguiner, G. *Tetrahedron.* **2001**, *57*, 4059; (d) Turck, A.; Ple, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489; (e) Epsztajn, J.; Marsais, F.; Quéguiner, G.; Snieckus, V. *Adv. Heterocycl. Chem.* **1991**, *52*, 187.

8. Reed, J. N.; Rotchford, J.; Strickland, D. *Tetrahedron Lett.* **1988**, *29*, 5725.

9. Prepared via a modified literature method, see: Kelly, T. A.; McNeil, D. W. *Tetrahedron Lett.* **1994**, *35*, 9003.

10. Hands, D.; Bishop, B. C.; Cameron, M.; Edwards, J. S.; Cottrell, I. F.; Wright, S. H. B. *Synthesis* **1996**, 877.

11. Cooling the dianion mixture to −78 °C prior to alkylation is necessary to prevent the formation of a dimeric species analogous to compound **6**.

12. The pivaloyl protecting group is equally effective in the alkylation step, but failed to give any of the cyclisation products on warming. Pivaloyl protected aminopyridines have been used in DoM reactions previously, see: Turner, J. A. *J. Org. Chem.* **1983**, *48*, 3401.

13. Compound **2f**: To a stirred solution of TMEDA (22.4 g, 0.192 mol) in THF (200 mL) at −20 °C was added *n*-BuLi (77 mL, 0.192 mol, 2.5 M in hexanes) over 10 min. The solution was stirred between −20 and 10 °C for 30 min and then cooled to −78 °C. A solution of 1,1-dimethylethyl[6-chloro-2-pyridinyl]carbamate **1b** (20.0 g, 0.087 mol) in THF (100 mL) was added over 15 min. The reaction mixture was aged for 1 h and then CuI (16.7 g, 0.088 mol) added in one portion. The reaction mixture was allowed to warm to −50 °C and aged at that temperature for 1 h. 1-Chloro-4-iodobutane (28.7 g, 0.131 mol) was added neat

over 1 min, the cooling bath removed and the reaction mixture allowed to warm to ambient. The reaction mixture was then refluxed for 9 h. The cooled reaction mixture was quenched by the addition of saturated sodium bicarbonate (100 mL). The aqueous layer was separated and extracted with isopropyl acetate (100 mL). The combined organic layers were washed sequentially with 20% w/w sodium thiosulfate (3×100 mL) and water (100 mL) and then concentrated to afford crude **2f**. Yield by HPLC assay was 90%. Purification by silica gel chromatography (eluent, hexanes:EtOAc 85:15), yielded 21.3 g of **2f** (86%) mp 166–168 °C (EtOAc); R_f 0.15 (hexanes:EtOAc 85:15); ^{1}H NMR (400 MHz, DMSO-d_6, 343 K): δ 7.62 (d, $J = 7.9$ Hz, 1H), 7.17 (d, $J = 7.9$ Hz, 1H), 3.35 (m, 2H), 2.58 (m, 2H), 1.62 (m, 2H), 1.51 (m, 2H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, 343 K): δ 155.7, 153.8, 146.7, 142.8, 134.0, 123.3, 80.6, 47.1, 32.6, 29.5, 28.8, 25.7; Anal. Calcd for $C_{13}H_{17}ClN_2O_2$: C, 59.47; H, 6.77; N, 9.91; Cl, 12.54. Found: C, 59.57; H, 6.79; N, 9.85; Cl, 12.53.

14. The role of additives and the directing group in DoM reactions is still the subject of intense research, see: (a) Rutherford, J. L.; Hoffman, D.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 8640; (b) Chadwick, S. T.; Rennels, R. A.; Rutherford, J. L.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 8640.

15. For examples of DoM reactions followed by lithium–copper transmetallation, see: (a) Kamila, S.; Chandrani, M.; De, A. *Tetrahedron Lett.* **2001**, *42*, 5955; (b) Cambie, R. C.; Hill, J. H. M.; Rutledge, P. S.; Stevenson, R. J.; Woodgate, P. D. *J. Organomet. Chem.* **1994**, *474*, 31.