First C-3 lithiation of DMAP: a new entry into chemical tuning of acylation catalysts†

Philippe C. Gros,*[a] Abdelatif Doudouh[a] and Christopher Woltermann[b]

Received (in Cambridge, UK) 11th April 2006, Accepted 9th May 2006
First published as an Advance Article on the web 22nd May 2006
DOI: 10.1039/b605170g

A $TMSCH_2Li$-based reagent promoted the first C-3 lithiation of DMAP opening a direct access to functional diversity in acylation catalysts.

4-Dimethylaminopyridine (DMAP) (**1**) is a well-known acylation catalyst. Numerous reviews have pointed out the important contribution of this organocatalyst to synthetic organic chemistry.[1] From pioneering works to the present, efforts have been made to elaborate more sophisticated analogues of **1**. The amino part has received attention in terms of electronic properties and chirality and its modification is well documented.[2]

The incorporation of chiral moieties at the C-3 or C-2 position of the pyridine ring has been the focus of much attention. The C-2 position has been functionalized using two lithiation methodologies. Vedejs and Chen exploited Kessar's strategy (BF_3 complexation and LiTMP lithiation)[3] to introduce carbonyl compounds at C-2.[4] This reaction was recently performed in a more practical and selective way using the BuLi/LiDMAE (LiDMAE = $Me_2N(CH_2)_2OLi$) superbase. A strong coordination of lithium by pyridine nitrogen and subsequent aggregate formation placed *n*-BuLi in adequate position for H-2 proton abstraction.[5]

In contrast, the abstraction of H-3 protons by lithium bases has not been reported due to the low efficiency of Me_2N– to orthodirect the reaction.[6] From our knowledge, only a trifluoroacetic group[7] and bromine[8] have been introduced by heating **1** with trifluoroacetyl anhydride or bromine, respectively, in basic media. While the 3-bromo derivative has been submitted with success to cross-couplings by Spivey *et al.*,[9] more doubtful was the effectiveness of the bromine–lithium exchange which was reported to work fairly well by Vedejs and coworkers[10] and sluggishly by Levacher and coworkers, who turned to bromine–magnesium exchange.[11]

Taking into account these limitations in reactivity and substitution diversity, the development of a general methodology for the direct introduction of functionalities at C-3 of DMAP remains a challenging synthetic goal. Thanks to electronic delocalisation as attested by charge calculations (PM3 semiempirical method), the H-3 proton exhibits the highest acidity (Fig. 1). Thus one could conceive of realizing the deprotonation at C-3 by an appropriate choice of reagent and conditions.

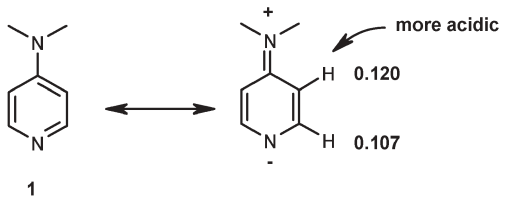
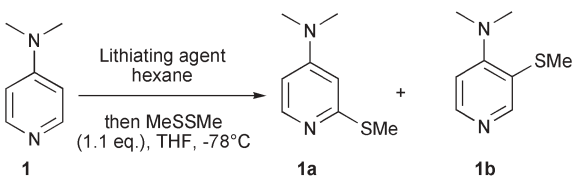


Fig. 1 PM3 calculated charge on H-3 and H-2 protons.

Herein is reported the first direct regioselective C-3 lithiation of DMAP using a $TMSCH_2Li$/LiDMAE combination in hexane–THF. A generally applicable methodology is disclosed for the preparation of valuable C-3 functional derivatives in good yields.

In the course of a research program aiming at the discovery of new efficient superbasic reagents, we studied the reaction of **1** with various $TMSCH_2Li$/LiDMAE combinations in hexane (Scheme 1, Table 1).

We were surprised to observe that in contrast with BuLi/LiDMAE which gave exclusive C-2 lithiation (entry 1),[5] the C-3 lithiation was observed in significant amount (entries 3 and 4). This meant that $TMSCH_2Li$ was probably not completely chelated by both LiDMAE and pyridine nitrogen allowing C-3 lithiation to occur. Interestingly, LiDMAE activated $TMSCH_2Li$ since the latter was found to be inert when used alone (entry 2).



Scheme 1 Lithiation of **1** under various conditions.

Table 1 Lithiation of **1** in hexane[a]

Entry	RLi (eq.)	LiDMAE (equiv.)	Conv. (%)	**1a**[b] (%)	**1b**[b] (%)
1	BuLi (2)	2	100	96[c]	—
2	$TMSCH_2Li$ (2)	—	0[d]	—	—
3	$TMSCH_2Li$ (2)	1	37	18	18
4	$TMSCH_2Li$ (2)	2	60	44	15

[a] Metallation performed on 1.84 mmol of **1** in hexane at r.t. for 4 h. [b] Isolated yields. [c] Metallation at 0 °C for 1 h. [d] No reaction occurred.

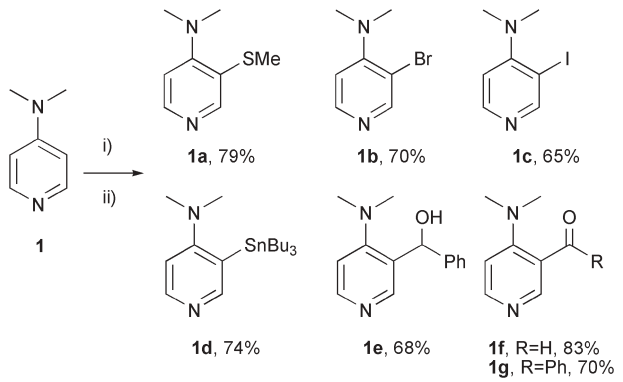
[a]*Synthèse Organométallique et Réactivité, UMR CNRS-UHP 7565 Université Henri Poincaré, Faculté des Sciences, Boulevard des Aiguillettes, 54506 Vandoeuvre-lès-Nancy, France. E-mail: philippe.gros@sor.uhp-nancy.fr; Fax: +33 3836 84785; Tel: +33 3836 84979*
[b]*FMC Corporation, Lithium Division, Highway 161 Box 795, Bessemer City, NC, 28016, USA. E-mail: CHRIS_WOLTERMANN@fmc.com; Fax: +1 704 868 5496; Tel: +1 704 868 5421*

† Electronic supplementary information (ESI) available: Experimental procedures and characterization of compounds **1a–g**. See DOI: 10.1039/b605170g

Table 2 Lithiation of **1** with $TMSCH_2Li$-based reagents in hexane–THF[a]

Entry	$TMSCH_2Li$ (equiv.)	LiDMAE (equiv.)	Additive (equiv.)	Conv. (%)	**1a**[b] (%)	**1b**[b] (%)
1	1	0	—	55	—	55
2	1	0.05	—	51	—	50
3	1	—	DIA (0.05)[c]	50	—	49
4	1	1	—	49	—	48
5	2	0	—	56	—	55
6	2	1	—	86	—	**85**
7	2	2	—	76	—	75
8	2	—	TMEDA (2)	79	—	70

[a] Metallation performed on 1.84 mmol of **1** in hexane–THF (1 : 1) at 0 °C for 4 h. [b] GC yields. [c] DIA: Diisopropylamine.



Scheme 2 Preparation of C-3 functional 4-DMAP. *Reagents and conditions*: (i) $TMSCH_2Li$ (2 equiv.)–LiDMAE (1 equiv.), hexane–THF, 0 °C, 4 h; (ii) MeSSMe, CBr_4, I_2, $ClSnBu_3$, PhCHO, $–(CH_2)_5–NCHO$ or $PhCONMe_2$ (1.1 equiv.), THF, −78 °C, 1 h then r.t.

From these results, we guessed that preventing the formation of aggregates between pyridine nitrogen and the lithiating agent using a strongly coordinating solvent could direct the reaction towards the C-3 lithiation. We found that THF nicely accomplished this task since the metallation performed in a hexane–THF mixture resulted in exclusive C-3 lithiation (Table 2). This reactivity in THF was in sharp contrast with those of lithium dialkylamides LDA or LiTMP which failed in lithiating **1** while BuLi/LiDMAE gave nucleophilic addition.[5]

Thus $TMSCH_2Li$ was found to be sufficiently basic and non-nucleophilic to perform the clean abstraction of the more acidic H-3 proton even when used in stoichiometric amount (entry 1). The incorporation of 1–2 equiv. of LiDMAE or TMEDA dramatically improved the yields with **1b** formed exclusively in 70–85% yields. However, the TMEDA-containing mixtures exhibited poor solubility complicating the stirring process and lowering the yield. Extended reaction times did not give higher yields probably due to a partial protonation of the intermediate 3-lithiopyridine by THF. The $TMSCH_2Li$/LiDMAE (2 : 1) combination offered the best result yielding **1b** in 85% yield as a single product (entry 6).

Then the above conditions were applied for investigating the scope of this new lithiation.‡ The reaction was then examined using several electrophilic reagents with the aim to introduce synthetically useful functionalities suitable for cross-couplings or asymmetric transformations (Scheme 2). A range of C-3 functional derivatives has been prepared efficiently using only a stoichiometric amount of electrophile in each case even for sensitive moieties such as aldehyde[12] or tin halide indicating the very low nucleophilicity of the basic reagent.

In summary, the first direct C-3 lithiation of DMAP has been realized. The $TMSCH_2Li$/LiDMAE reagent effected a highly regioselective metallation process when used in a hexane–THF medium. When compared with current methodologies that allow the introduction of only a few substituents, this lithiation is of particular interest to design new DMAP-based acylation catalysts by broadening functional diversity.

The authors would like to thank FMC Corporation, Lithium Division for financial support and Sandrine Adach (Nancy) for recording the mass spectra.

Notes and references

‡ *General procedure* for C-3 functionalisation of **1**. $TMSCH_2Li$ (6 mL of a 0.92 M solution in hexane, 5.52 mmol) was added dropwise to a solution of 2-dimethylaminoethanol (164 mg, 1.84 mmol) in hexane (6 mL) at 0 °C. After 30 min of stirring, a solution of **1** (1.84 mmol) in THF (12 mL) was then added dropwise. The solution was then stirred for 4 h at the same temperature then treated at −78 °C with a solution of the appropriate electrophile (2.02 mmol) in THF (1 mL). The temperature was maintained at −78 °C for 1 h and at 0 °C for 30 min. Hydrolysis was then performed at this temperature with water (10 mL). Then the reaction medium was extracted twice with diethyl ether (25 mL), the organic layer dried over $MgSO_4$ and evaporated under vacuum. Finally, the crude product was subjected to GC analysis and purified by column chromatography eluting with hexane–AcOEt mixtures. See ESI† for characterization of compounds **1a–g**.

1 G. Höfle, W. Steglich and H. Vorbruggen, *Angew. Chem.*, 1978, **90**, 602; G. Höfle, W. Steglich and H. Vorbruggen, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 569; F. V. Scriven, *Chem. Soc. Rev.*, 1983, **12**, 129; U. Ragnarsson and L. Grehn, *Acc. Chem. Res.*, 1998, **31**, 494; R. Murugan and E. F. V. Scriven, *Aldrichimica Acta*, 2003, **36**, 21.

2 A. Spivey, A. Maddaford, T. Fekner, A. J. Redgrave and C. S. Frampton, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3460; S. Wagaw and S. L. Buchwald, *J. Org. Chem.*, 1996, **61**, 7240; J. P. Wolfe and S. L. Buchwald, *J. Am. Chem. Soc.*, 1997, **119**, 6054; H. Hotsuki, H. Sakai and T. Shinohara, *Synlett*, 2000, 116.

3 For a review on BF_3-assisted lithiations, see: S. Kessar and P. Singh, *Chem. Rev.*, 1997, **97**, 721, and references therein.

4 E. Vedejs and X. Chen, *J. Am. Chem. Soc.*, 1996, **118**, 1809.

5 D. Cuperly, Ph. Gros and Y. Fort, *J. Org. Chem.*, 2002, **67**, 238. For related work, see also: F. Louërat, Ph. Gros and Y. Fort, *Tetrahedron*, 2005, **61**, 4761; D. Martineau, M. Beley and Ph. C. Gros, *J. Org. Chem.*, 2006, **71**, 566.

6 For an evaluation of the orthodirecting ability of heteroaromatic substituents in lithiation, see: V. Snieckus, *Chem. Rev.*, 1990, **90**, 879.

7 M. Kawase, J. Koyanagi and S. Saito, *Chem. Pharm. Bull.*, 1999, **47**, 718.

8 W. W. Paudler and M. V. Jovanovic, *J. Org. Chem.*, 1983, **48**, 1064; M. P. Groziak and L. M. Melcher, *Heterocycles*, 1987, **26**, 2905.

9 A. C. Spivey, T. Fekner, S. E. Spey and H. Adams, *J. Org. Chem.*, 1999, **64**, 9430.

10 S. A. Shaw, P. Aleman and E. Vedejs, *J. Am. Chem. Soc.*, 2003, **125**, 13368.

11 T. Poisson, M. Penhoat, C. Papamicaël, G. Dupas, V. Dalla, F. Marsais and V. Levacher, *Synlett*, 2005, **15**, 2285.

12 Compound **1f** has been prepared in 45% yield by C-3 lithiation of 4-fluoropyridine and subsequent quenching with DMF, see: F. Marsais, F. Trécourt, P. Bréant and G. Quéguiner, *J. Heterocycl. Chem.*, 1988, **25**, 81.

