Synthesis of 2,5-Diiodopyrazine by Deprotonative Dimetalation of Pyrazine

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Abstract: The deproto-metalation reactions of pyrimidine and pyrazine were regioselectively carried out using lithium tris(2,2,6,6-tetramethylpiperidino)cadmate in tetrahydrofuran at room temperature. This result was demonstrated by subsequent trapping with iodine to afford 4-iodopyrimidine and 2-iodopyrazine in 71% and 63% yields, respectively. The same reaction performed on pyridazine afforded a mixture of the 3- and 4-iodo derivatives (55% and 41% yields, respectively). From pyrazine, access to the 2,5-diiodo derivative (40% on a 25 mmol scale) proved possible using a larger amount of base (1 equiv instead of 0.33).

Key words: metalations, cadmium, lithium, heterocycles, iodine

Introduction

The preparation of functionalized diazines is an important synthetic goal because of the multiple applications of these molecules.1

Deprotonative metalation has been widely used as a powerful method for the regioselective metalation of aromatic rings and various strong bases, such as alkyllithiums and lithium dialkylamides, have been employed for this purpose.2 Even with the latter, either extremely low reaction temperatures or in situ electrophilic trapping are required for aromatics bearing reactive functions (e.g., ester or cyano groups) or sensitive π-deficient heterocycles due to the high reactivity of the corresponding (hetero)aryllithiums.

The use of additives for lithium compounds in order to modify their behavior (‘synergy’) is a challenging field. Various R2MLi type compounds have been prepared, with such species exhibiting properties that cannot be attained by the homometallic compounds on their own.

Well-known examples are the powerful mixtures of organolithiums and alkoxides (M = alkali metal) described by Schlosser,3 Lochmann,4 and Caubère.5

More recently, RnMLi type compounds (M = nonalkali metal) have been developed. These species, present in stoichiometric6 or catalytic7 amounts in the reaction mixture, display a large panel of reactivity depending on both the metal M and the groups connected to it. By combining soft organometallic compounds with alkali additives such as lithium 2,2,6,6-tetramethylpiperidino (LiTMP) or lithium chloride, bases [t-Bu2Zn(TM)P]Li8 and (TMP)2Zn2 MgCl2·2 LiCl;TMP = 2,2,6,6-tetramethylpiperidino] have been prepared and used for the deproto-metalation of sensitive aromatic substrates.

The metation of diazines is a difficult challenge due to very facile nucleophilic addition reactions in relation with the low LUMO energy levels of these substrates. Recourse to hindered dialkylamides such as lithium diisopropylamide and lithium 2,2,6,6-tetramethylpiperidide allowed numerous substituted diazines to be deprotonated.9 Without substituents, reactions are less obvious. Metatation of pyrazine and pyridazine was found possible using excess lithium 2,2,6,6-tetramethylpiperidide and very short reaction times at very low temperatures, while metation of pyrimidine could only be accomplished using the in situ trapping technique.10 Kondo described in 2003 the unprecedented regioselective functionalization of pyridazine and pyrimidine at positions 4 and 5, respectively, using hindered phosphazene t-BuP4 base and zinc(II) iodide as an additive in toluene, and in the presence of a carbonylated compound as electrophile.11
Knochel has reported, since 2006, the use of mixed lithium–magnesium amides, such as (TMP)MgCl-LiCl, for the deprotonation of diazines;\textsuperscript{7a,12} the method is powerful, but it still requires low temperatures, and has not been used for unsubstituted substrates.

We recently observed that the metalation of all the unsubstituted diazines could be performed at room temperature or more in tetrahydrofuran using a mixture of bis(2,2,6,6-tetramethylpiperidino)zinc and lithium 2,2,6,6-tetramethylpiperidide (0.5 equiv each) [prepared in situ from ZnCl$_2$·TMEDA\textsuperscript{13} (0.5 equiv) and LiTMP (1.5 equiv)] a result evidenced by trapping with iodine (Scheme 2).\textsuperscript{14}

In order to seek out a more efficient reagent to deprotonate diazines, we focused on the reaction using the corresponding mixture with cadmium instead of zinc.\textsuperscript{15} Indeed, Wittig and co-workers observed in 1951 that the efficiency of deprotonation reactions of fluorene using different Ph$_3$MLi reagents was in relation to the size of the central metal M. In particular, quenching with carbon dioxide and subsequent acidic work-up afforded diphenylacetic acid in a low 16% yield after ten days reaction time using lithium triphenylzincate (Ph$_3$ZnLi) as a base whereas a satisfying 64% yield was obtained after three days using lithium triphenylcadmate (Ph$_3$CdLi).\textsuperscript{16}

In contrast to the corresponding Zn–Li base, the in situ prepared mixture of cadmium(II) chloride–N,N,N’,N’-tetramethylethylenediamine (CdCl$_2$·TMEDA)\textsuperscript{17} and lithium 2,2,6,6-tetramethylpiperidide (3 equiv) seems to provide a lithium ‘ate’ compound.\textsuperscript{15}

**Scope and Limitations**

Attempts to metatelate pyridazine, pyrimidine, or pyrazine indicated that the Cd–Li base was suitable for an efficient reaction in tetrahydrofuran at room temperature. Indeed, subsequent trapping with iodine after two hours afforded substituted derivatives in satisfying yields. Whereas 4-iodopyrimidine (3) was regioselectively formed from pyrimidine (x = 0.5), a mixture of 3-iodopyridazine (2a) and 4-iodopyridazine (2b) was obtained from pyridazine (x = 1) in a ~60:40 ratio (Scheme 3).

Reactions were performed under an argon atmosphere. THF was distilled over sodium/benzophenone. Liquid chromatography separations were achieved on silica gel Merck Geduran Si 60 (40–63 μm). Melting points were measured on a Kofler apparatus. $^1$H and $^{13}$C NMR were recorded at 200 and 50 MHz, respectively, on a Bruker ARX-200 spectrometer. Chemical shifts are given in ppm relative to the solvent residual peak (H) and the central peak of the solvent signal ($^{11}$C).\textsuperscript{23} IR spectra were taken on a Perkin-Elmer Spectrum 100 spectrometer. HRMS measurements and elemental analyses were performed at the CRMPO in Rennes (Centre Régional de Mesures Physiques de l’Ouest) using a Micromass MS/MS ZABSpec TOF instrument in EI mode and a Thermo-Finnigan Flash EA 1112 CHNS analyzer, respectively.

2-Iodopyrazine (4) was isolated in 63% yield using cadmium(II) chloride–N,N,N’,N’-tetramethylethylenediamine (x = 0.33) (0.33 equiv) and lithium 2,2,6,6-tetramethylpiperidide (1 equiv). If the amounts of cadmium(II) chloride–N,N,N’,N’-tetramethylethylenediamine and lithium 2,2,6,6-tetramethylpiperidide are increased to 0.5 equivalent and one equivalent, respectively, 2,5-diodopyrazine (1) concomitantly forms (20% yield) to the detriment of 2-iodopyrazine (4) (59% yield).

The formation of dimetalated species has been described using zincate\textsuperscript{18} or manganate\textsuperscript{19} type bases; hence, the use of one equivalent of cadmium(II) chloride–N,N,N’,N’-tetramethylethylenediamine and three equivalents of lithium 2,2,6,6-tetramethylpiperidide was used to deprotonate pyrazine. Under the same reactions conditions, the diiodide 1 was isolated in 58% yield when the reaction was performed on a 2-mmol scale. The protocol could be successfully transposed to a 25-mmol scale, albeit providing compound 1 in a lower yield of 40% (Scheme 1).

To our knowledge, the synthesis of 2,5-diodopyrazine (1) has not been reported by other methods. Similar compounds such as 2-bromo-5-iodopyrazine\textsuperscript{20} and 2,5-dibromopyrazine\textsuperscript{21} have previously been prepared by diazotization of 5-bromopyrazinamine (41% and 66% yield, respectively), the latter being accessible by bromination of pyrazinamine (75% yield).\textsuperscript{22}

Such compounds can find application as substrates for the synthesis of molecules endowed with biological\textsuperscript{23} or photophysical\textsuperscript{24} properties.
Gram-Scale Synthesis of 2,5-Diiodopyrazine (1)

To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (13 mL, 75 mmol) in THF (25 mL) were successively added 1.6 M BuLi in hexanes (75 mmol) and CdCl2·TMEDA (7.5 g, 25 mmol). The mixture was stirred at 0 °C for 15 min before introduction of pyrazine (2.0 g, 25 mmol). After 2 h at r.t., a solution of I2 (14 g, 75 mmol) in hexanes (75 mmol) and CdCl2·TMEDA (7.5 g, 25 mmol). The mixture was stirred overnight before addition of sat. aq Na2S2O3 (40 mL) and extraction with EtOAc (3 × 40 mL). The combined organic layers were dried (MgSO4), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica gel, heptane–CH2Cl2, 100:0 to 80:20) gave 2,5-diiodopyrazine (3.3 g, 40%) as a yellow powder; mp 141 °C.

IR (ATR): 3048, 1431, 1421, 1384, 1267, 1121, 1104, 1004, 886 cm⁻¹.
1H NMR (CDCl3): δ = 8.63 (s, 2 H).
13C NMR (CDCl3): δ = 116.6 (C2 and C5), 154.1 (C3 and C6).

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References