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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 tri(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 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, the access to the 2,5-dioido derivative (40% on a 25 mmol scale) proved possible using a larger amount of base (1 equiv instead of 1/3).

Key words: Metalations, Cadmium, Lithium, Heterocycles, Iodine.

Procedure 1

\[
\begin{align*}
1) & \quad 1 \text{ equiv CdCl}_2 \cdot \text{TMEDA} + 3 \text{ equiv LiTMP} \\
& \quad \text{THF}, \text{ rt}, 2 \text{ h} \\
2) & \quad 25 \text{ mmol scale} \\
& \quad 40\% \text{ yield}
\end{align*}
\]

Introduction

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

Deprotonative metathesis has been widely used as a powerful method for the regioselective metalation of aromatic rings, and various strong bases such as alkylolithiums 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 \(R_n\)MLLi-type compounds have been prepared, 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 Lochmann4 and Caubère5.

More recently, \(R_n\)MLLi-type compounds (M = non-alkali metal) have been developed. These species, present in stoichiometric6 or catalytic7 amount in reaction mixtures, display a large panel of reactivities depending on both the metal M and the groups connected to it.

By combining soft organometallic compounds with alkali additives such as LiTMP (TMP = 2,2,6,6-tetramethylpiperidino) or LiCl, bases (\(\text{Bu}_2\)Zn(TMPLi)8 and (TMP)Li-Zn-2 MgCl2-2 LiCl79 respectively) have been prepared and used for the deproto-metalation of sensitive aromatic substrates.

Metalation 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 (LiDA) and lithium 2,2,6,6-tetramethylpiperidide (LiTMP) allowed numerous substituted diazines to be deprotoonated.9 Without substituent, reactions are less obvious. Metalation of pyrazine and pyridazine was found possible with an excess of LiTMP and very short reaction times at very low temperatures, while metalation 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 \(\text{Bu}-\text{P}4 \text{ base and ZnI}_2\) as 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 deprotoation of diazines;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 (THF) using a mixture of (TMP)Zn and LiTMP (0,5 equiv each), in situ prepared from ZnCl2-TMEDA13 (0,5 equiv) and LiTMP (1,5 equiv), a result evidenced by trapping with iodine (Scheme 1).14

![Scheme 1](attachment:image.png)
In order to seek out a more efficient reagent to deproto-
matalate diazines, we focused 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\textsubscript{3}MLi reagents was in relation with the size of the
central metal M. In particular, quenching with CO\textsubscript{2}
and subsequent acidic work-up afforded diphenylene-
cetic acid in a low 16\% yield after 10 days reaction time
using Ph\textsubscript{3}ZnLi as base whereas a satisfying 64\% yield
was obtained after 3 days using Ph\textsubscript{3}CdLi.\textsuperscript{16}

In contrast to the corresponding Zn-Li base, the \textit{in situ}
prepared mixture of CdCl\textsubscript{2}-TMEDA\textsuperscript{17} and LiTMP (3
equiv) seems to provide a lithium ate compound.\textsuperscript{15}

**Scope and Limitations**

Attempts to metalate pyridazine, pyrimidine or pyrazine
indicated that the Cd-Li base was suitable for an efficient
reaction in THF at room temperature. Indeed, subsequent
trapping with iodine after 2 h afforded substituted deri-
vatives in satisfying yields. Whereas 4-iodopyrimidine
(2) was regioselectively formed from pyrimidine (x =
0.5), a mixture of 3- and 4-iodopyridazine (1\textsubscript{a,b})
was obtained from pyridazine (x = 1) in a 60/40 ratio
(Scheme 2).

![Scheme 2](image)

Scheme 2 \^ \textsuperscript{a} x = 1. \^ \textsuperscript{b} x = 0.5. \^ \textsuperscript{c} x = 0.33.

Iodopyrazine (3) was isolated in 63\% yield using
CdCl\textsubscript{2}-TMEDA (x = 0.33 equiv) and LiTMP (3x = 1
equiv). If the amounts of CdCl\textsubscript{2}-TMEDA and LiTMP go
into 0.5 equiv and 1 equiv, respectively, 2,5-diiodopyrazine (4)
concomitantly forms (20\% yield) to the detriment of iodopyrazine (3) (59\% yield).

The formation of dimetalated species being described
using zinicate\textsuperscript{18} or manganese\textsuperscript{19} type bases, the use of 1
equiv of CdCl\textsubscript{2}-TMEDA and 3 equiv of LiTMP was
attempted to deprotonate pyrazine. Under the same
reactions conditions, the diiodide 4 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 4 in a lower yield of
40\% (Scheme 3).

![Scheme 3](image)

Scheme 3 \^ \textsuperscript{a} 2 mmol scale. \^ \textsuperscript{b} 25 mmol scale.

To our knowledge, the synthesis of 2,5-diiodopyrazine
(4) has never 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
diazonization of 5-bromopyrazinamine (41\% and 66\% yield,
respectively), the latter being accessible by bromi-
nation of pyrazinamine (75\% yield).\textsuperscript{22}

Such compounds can find applications as substrates for
the synthesis of molecules endowed with biological\textsuperscript{23}
or photophysical\textsuperscript{24} properties.

Reactions were performed under argon atmosphere. THF was
distilled over sodium/benzophenone. Liquid chromatography
separations were achieved on silica gel Merck Gedaru S 60 (40–
63 \textmu m). Melting points were measured on a Kofler apparatus. \textsuperscript{1}H
and \textsuperscript{13}C Nuclear Magnetic Resonance (NMR) spectra were record-
ed at 200 and 50 MHz, respectively, on a Bruker ARX-200 spec-
trometer. \textsuperscript{1}H chemical shifts (\delta) are given in ppm relative to the
solvent residual peak, and \textsuperscript{13}C chemical shifts relative to the cen-
tral peak of the solvent signal.\textsuperscript{25} IR spectra were taken on a Perkin
Elmer Spectrum 100 spectrometer. High resolution mass spectra
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 instru-
ment in EI mode and a Thermo-Finnigan Flash EA 1112 CHNS analyzer,
respectively.

**Gram-Scale Synthesis of 2,5-Diiodopyrazine (4).**

To a stirred, cooled (0 °C) solution of 2,2,6,6-
tetramethylpiperidine (13 mL, 75 mmol) in THF (25 mL)
were successively added BuLi (1.6 M hexanes solution, 75 mmol)
and CdCl\textsubscript{2}-TMEDA (7.5 g, 25 mmol). The mixture was stirred for 15
min at 0 °C before introduction of pyrazine (2.0 g, 25 mmol). After 2 h at room
temperature, a solution of I\textsubscript{2} (14 g, 75 mmol) in
THF (25 mL) was added. The mixture was stirred overnight
before addition of an aqueous saturated solution of Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} (40 mL)
and extraction with AcOEt (3 \times 40 mL). The combined organic
layers were dried over MgSO\textsubscript{4}, filtered and concentrated under
reduced pressure. Purification by flash chromatography on silica
gel (eluent: heptane/CH\textsubscript{2}Cl\textsubscript{2} 100/0 to 80/20) gave 3.3 g (40\%)
of 2,5-diiodopyrazine as a yellow powder.

M\textsubscript{p} 141 °C.

\textsuperscript{1}H NMR (CDCl\textsubscript{3}): \delta 8.63 (s, 2H).

\textsuperscript{13}C NMR (CDCl\textsubscript{3}): \delta 116.6 (C\textsubscript{2} and C\textsubscript{3}), 154.1 (C\textsubscript{4} and C\textsubscript{5}).

IR (ATR): \nu 3048, 1431, 1421, 1384, 1267, 1121, 1104, 1004 and
886 cm\textsuperscript{-1}.

HRMS: calecd for C\textsubscript{4}H\textsubscript{5}I\textsubscript{2}N\textsubscript{2}: 331.8307, found: 331.8297.

Anal. Calecd for C\textsubscript{4}H\textsubscript{5}I\textsubscript{2}N\textsubscript{2}: C, 14.48; H, 0.61; N, 8.44. Found: C,
14.31; H, 0.69; N, 8.48.
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References

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