Pergamon

Tetrahedron Letters 40 (1999) 4339–4342

TETRAHEDRON LETTERS

Pyridylmagnesium Chlorides from Bromo and Dibromopyridines by Bromine-Magnesium Exchange: A Convenient Access to Functionalized Pyridines

François Trécourt, Gilles Breton, Véronique Bonnet, Florence Mongin, Francis Marsais and Guy Quéguiner*

Laboratoire de Chimie Organique Fine et Hétérocyclique, IRCOF,
Place E. Blondel, BP 08, 76131 Mont-Saint-Aignan (France)

Received 18 February 1999; accepted 17 April 1999

Abstract: *Various bromopyridines were converted to the corresponding pyridylmagnesium chlorides at room temperature by treatment with iPrMgCl. The resulting Grignard reagents were quenched by various electrophiles to afford functionalized pyridines. The bromine-magnesium exchange of some dibromopyridines was also studied.* © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: *Pyridine; Grignard reagents; Exchange reaction; Regioselection*

Lithiation is an important method for the preparation of polyfunctional pyridines since lithiated pyridines display a high reactivity toward many electrophilic functions.[1] This methodology often requires low temperatures which are not easy to realize on an industrial scale. Bromine-lithium exchange[1a-2] has to be usually performed at low temperature (-100 °C in THF or around -40 °C in diethyl ether) because of side-reactions such as deprotonation, addition to the substrate, elimination of lithium bromide (to give pyridynes), bromine migration ("dance") or even ring opening reactions.

Transmetallation from lithiated pyridines is also used to allow coupling reactions with various substrates; as an example, caerulomycin C could be successfully synthesized *via* a pyridylzinc halide.[3]

We have been interested in the development of pyridylmagnesium reagents that could be involved either of electrophilic trapping and coupling reactions and thus allow the synthesis of various substituted pyridines. It is well established that the direct access to pyridine Grignard reagents by action of magnesium fails; it can be somewhat improved by the activation of magnesium with a more reactive bromide *via* a bromine-magnesium exchange reaction.[4]

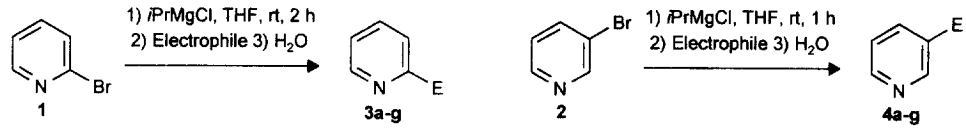
A survey of the literature revealed that some iodopyridines undergo smooth iodine-magnesium exchange when treated with alkyl or phenylmagnesium halides.[5] Few significant results were reported from chloro- and bromopyridines, except those of Paradies[6] and Meunier.[7] Paradies describes bromine and chlorine-magnesium exchange with phenylmagnesium halides but the results could not be repeated.[5a] Meunier obtained bromine-magnesium exchange when isopropylmagnesium chloride was used in tetrahydrofuran at -25 °C but no trapping of the resulting Grignard derivatives was attempted with electrophiles.

* Fax: +33 (0) 2 35 52 29 62 ; e-mail: <guy.queguiner@insa-rouen.fr>

PII: S0040-4039(99)00789-3

Since iodopyridines are not easily accessible, a study of commercially available bromopyridines[8] was undertaken. Various alkylmagnesium chlorides, reaction times, solvents and magnesium complexing agents were tested in order to optimize the exchange conditions and the trapping of the pyridine Grignard reagents with electrophiles; *i*PrMgCl was found to be the best exchange agent on bromo derivatives in THF. It was also demonstrated that the halogen of the pyridine Grignard reagent was chlorine.

2- and 3-Bromopyridines (**1-2**) were found to react smoothly with *i*PrMgCl in THF at room temperature. The intermediates were trapped with various electrophiles in moderate (in the case of disulfides and carbonyl compounds containing an α-hydrogen) to high yields with aldehydes and iodine. Yields are similar to those obtained through bromine-lithium exchange,[9] but the full process can be achieved at room temperature. Under these conditions, the overall reaction proves to be highly chemoselective and no side reactions product could be detected. It can be noted that the yield increases with the reactivity of the electrophile (Scheme 1, Table 1), which has been previously observed in the case of pyridyllithiums.



Scheme 1

Table 1. Trapping of 2- and 3-Pyridylmagnesium Chlorides with Various Electrophiles.

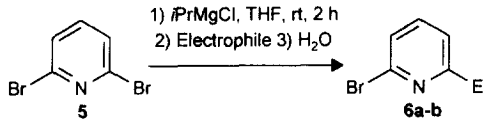
Starting material	Electrophile	E	Product Yield %	Starting material	Electrophile	E	Product Yield %
1	PhCHO	CH(OH)Ph	**3a**:[10a] 80	2	PhCHO	CH(OH)Ph	**4a**:[10f] 93[a]
1	CH_3CHO	$CH(OH)CH_3$	**3b**:[10a] 79	2	CH_3CHO	$CH(OH)CH_3$	**4b**:[10g] 74[b]
1	CH_3CH_2CHO	$CH(OH)CH_2CH_3$	**3c**:[10b] 54	2	*t*BuCHO	CH(OH)*t*Bu	**4c**:[10h] 78
1	CH_3COCH_3	$C(OH)(CH_3)_2$	**3d**:[10c] 30	2	EtCOEt	$C(OH)Et_2$	**4d**:[10i] 58
1	CH_3COCl	$COCH_3$	**3e**: 15	2	PhCOCl[c]	COPh	**4e**: 35
1	PhSSPh	SPh	**3f**:[10d] 45[a]	2	CH_3SSCH_3	SCH_3	**4f**:[10j] 58[a]
1	I_2	I	**3g**:[10c] 97	2	I_2	I	**4g**:[10k] 78

[a] 1 eq. of triethylamine was added before quenching with the electrophile; [b] 10 eq. of CH_3CHO were used at -20 °C; [c] addition of PhCOCl at -70 °C then the mixture was allowed to reach rt.

Concerning the exchange reaction on monobromopyridines, it could be observed that both 2- and 3-pyridylmagnesium chlorides can be easily prepared, but the first revealed to be less reactive with electrophiles. Due to its instability, 4-bromopyridine was not completely studied. Nevertheless, we could show that it undergoes bromine-magnesium exchange in the same way, and gives the corresponding alcohol[11] in 64% yield, after quenching with benzaldehyde.

This study was then extended to dibromopyridines with the purpose of studying the regioselectivity of the exchange.

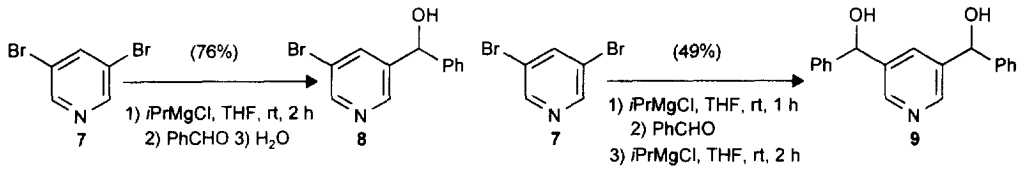
2,6-Dibromopyridine (**5**) reacts with *i*PrMgCl to give a single exchange reaction (even with an excess of reagent), as demonstrated by the trapping with benzaldehyde or iodine (Scheme 2).



Scheme 2

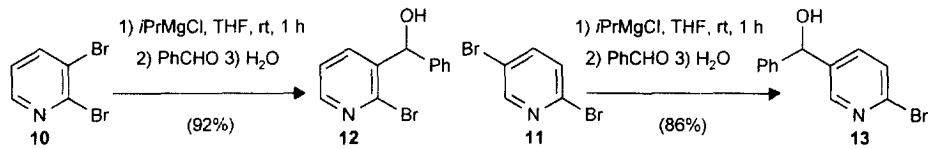
6a: E= CH(OH)Ph, 42% when 2 eq. of *i*PrMgCl and PhCHO were used.
6b: E= I, 90% when 4 eq. of *i*PrMgCl and I_2 were used.

A single exchange was also established from 3,5-dibromopyridine **7** and afforded alcohol **8**[12] in a satisfying yield of 76% after treatment with benzaldehyde. Consecutive exchange of the second bromine atom in a one-pot procedure allowed the synthesis of 3,5-disubstituted pyridine **9**[13] (Scheme 3).



Scheme 3

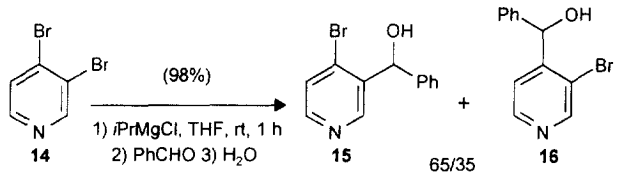
Reacting 2,3-[7] and 2,5-dibromopyridines (**10-11**) with *i*PrMgCl at room temperature followed by quenching with benzaldehyde, afforded respectively 3- and 5-substituted 2-bromopyridines **12**[9c] and **13**[14] in high yields. Exchange occurred at C3, as previously observed,[15] when treated with butyllithium in THF at -100 °C (Scheme 4).



Scheme 4

Exchange of the second bromine atom under various conditions remained unsuccessful.

3,4-Dibromopyridine (**14**) reacts in the same conditions to give exchange at C3 and C4 in an approximate ratio 65:35 respectively (Scheme 5).



Scheme 5

In conclusion, commercial *i*PrMgCl was suitable for a clean bromine-magnesium exchange on various bromo and dibromopyridines at room temperature in THF, whereas corresponding bromine-lithium exchange

has to be performed at very low temperature to prevent side reactions. The regioselectivity of the bromine-magnesium exchange seems to be the same to that of the bromine-lithium one *i.e.* C3 ~ C4 > C2. Some reactions involving pyridylmagnesium halides, such as cross coupling, are currently underway.

Bromine-magnesium Exchange; Typical Procedure: 3-Bromopyridine (0.96 mL, 10 mmol) was added to *i*PrMgCl (10 mmol) in THF (5 mL) at rt. After 1 h, benzaldehyde (10 mmol) was added. After 2 h at rt, water (50 mL) was added. Extraction with dichloromethane (3 x 20 mL), drying over magnesium sulphate and column chromatography using dichloromethane as an eluent afforded alcohol **4a** (84% yield).

Acknowledgment: We thank Frédéric Simian, Jérôme Mazajczyk, Olivier Marcq and Gérald Chaumaz for their contribution to this study.

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12. Compound **8** ^{1}H NMR ($CDCl_3$ at 200 MHz): 8.21 (s, 1H), 8.20 (s, 1H), 7.90 (s, 1H), 7.2 (m, 5H, Ph), 5.94 (s, 1H, OH), 5.66 (s, 1H).
13. Compound **9** ^{1}H NMR ($CDCl_3$ at 200 MHz): 8.50 (s, 2H), 7.90 (s, 1H), 7.3 (m, 10H, Ph), 6.25 (d, 2H, OH, J = 3.1), 5.85 (d, 2H, J = 3.1).
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