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Imidoyllithiums: Masked Acyllithium Reagents†

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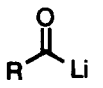
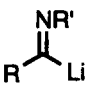
Abstract: The reaction of chloroimines **1** with an excess of lithium powder and a catalytic amount of naphthalene (4 mol %) in THF at -78°C leads to the corresponding imidoyllithium intermediates **2**, which by treatment with different electrophiles [Pr^{i}CHO, Bu^{t}CHO, n-C_5H_{11}CHO, PhCHO, Et_2CO, $(CH_2)_5CO$, EtOCOCl, MeOCSCl, n-C_7H_{15}CON(Me)OMe] at -78 to 20°C and final hydrolysis with water affords functionalysed imines **3**. For starting material **1a** is necessary to filter off the excess of lithium at the end of the lithiation step in order to get compounds **3**, without filtration amines **4** are the reaction products isolated. Hydrolysis of compounds **3** either during chromatographic purification or by acidic hydrolysis (2 N HCl, THF) gives the expected functionalised ketones **5**.

Acyllithium intermediates **I** are important reagents in synthetic organic chemistry due to their avility to transfer the acyl functionality to electrophilic reagents.[1] Since this type of reagents containing an electropositive metal such as lithium are very unstable, some alternatives have been developed to prepare synthetically equivalent intermediates, one of them being the corresponding imidolyl derivatives[2] of type **II**. Two different ways have been described to prepare these reagents: (a) tin-lithium exchange[3] and (b) addition of an organolithium reagent to an isonitrile.[4] In both cases the process is limited to *N*-aryl derivatives and in order to avoid *o*-lithiation is necessary to use the corresponding *N*-2,6-dimethylphenyl derivatives. In addition, the preparation of intermediates of type **II** by deprotonation is unknown and the only case of forming this type of reagents by chlorine- or iodine-lithium exchange using *n*-butyllithium has only been described for the corresponding trifluoromethyl derivative (**II** with R = CF_3).[5] On the other hand, in the last few years we have applied an arene-catalysed lithiation[6] for the preparation of very reactive functionalised organolithium compounds[7] (by chlorine-lithium exchange[8a,9] or by reductive opening of heterocyclic precursors[8b]) as well as the *in situ* preparation of polylithiated synthons.[8c] In this paper we report on the preparation for the first time of intermediates of type **II** by chlorine-lithium exchange using the mentioned arene-catalysed methodology.



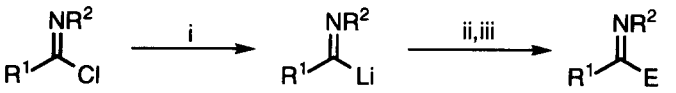
I



II

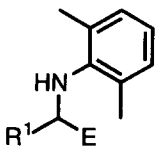
† This paper is dedicated to Prof. W. Adam on occasion of his 60th birthday.

The reaction of different chloroimines **1** with an excess of lithium powder and a catalytic amount of naphthalene (4 mol %) in THF at -78°C led to a solution of the corresponding intermediate **2**, which by treatment with an electrophile [PriCHO, ButCHO, *n*-$C_5H_{11}CHO$, PhCHO, Et_2CO, $(CH_2)_5CO$, EtOCOCl, MeOCSCl, *n*-$C_7H_{15}CON(Me)OMe$] at temperatures ranging between -78 and 20°C followed by hydrolysis with water afforded the expected compounds **3** (Scheme 1 and Table 1). In the case of the starting material **1a** was necessary to filter off the excess of lithium prior the addition of the electrophile in order to avoid the final reduction of the carbon-nitrogen double bond[10] (Table 1, entries 1-7): without the mentioned filtration compounds **4** were isolated in moderated yields (Table 2). On the other hand, compounds **4de,df** were isolated when starting from chloroimine **1d** and using ketones as electrophiles (Table 2, entries 3 and 4); for chloroformate or thiochloroformate derivatives, the expected compounds **3dg,dh** were isolated (Table 1, entries 14 and 15). In addition, for chloroimine **1b**, the corresponding products **3ba-be** derived from aldehydes were unstable: during the chromatographic purification only deprotected materials **5ba-be** were isolated (Table 1, entries 8-11).

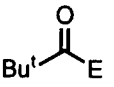


1a : R^1= Bu^t, R^2= 2,6-$Me_2C_6H_3$ **2** **3aa-dh**
1b : R^1= Bu^t, R^2= *n*-C_8H_{17}
1c : R^1= *n*-C_6H_{13}, R^2= 2,6-$Me_2C_6H_3$
1d : R^1= *c*-C_6H_{11}, R^2= 2,6-$Me_2C_6H_3$

Scheme 1. *Reagents and conditions*: i, Li, $C_{10}H_8$ cat. (4 mol %), THF, -78°C (then filtration at -78°C for compound **1a**); ii, E+ = PriCHO, ButCHO, *n*-$C_5H_{11}CHO$, PhCHO, Et_2CO, $(CH_2)_5CO$, EtOCOCl, MeOCSCl, *n*-$C_7H_{15}CON(Me)OMe$, -78 to 20°C; iii, H_2O.



4af : R^1= Bu^t, E = $(CH_2)_5COH$
4ag : R^1= Bu^t, E = EtOCO
4de : R^1= *c*-C_6H_{11}, E = Et_2COH
4df : R^1= *c*-C_6H_{11}, E = $(CH_2)_5COH$



5aa : E = PhCHOH
5af : E =$(CH_2)_5COH$
5ag : E = *n*-$C_7H_{15}CO$
5ba : E = PriCHOH
5bb : E = ButCHOH
5bc : E = *n*-$C_5H_{11}CHOH$
5be : E = PhCHOH

Starting chloroimines **1** were easily prepared from the corresponding amides by treatment with phosphorus pentachloride under toluene reflux.[11]

Hydrolysis of stable imines **3** can be easily carried out with 2 N hydrochloric acid overnight, so, for instance, compounds **3aa**, **3af** and **3ag** gave the corresponding functionalised ketones **5aa**, **5af** and **5ag**, respectively with ≥95% isolated yield.

Table 1. Preparation of Compounds **3**

Entry	Starting material	Electrophile E^+	Reaction conditions: Lithiation	Reaction conditions: S_E	Product[a]: No.	R^1	R^2	E	Yield (%)[b]	R_f[c]
1	**1a**	Pr^iCHO	-78°C/2 h[d]	-78→20°C/8 h	**3aa**	Bu^t	2,6-$Me_2C_6H_3$	Pr^iCHOH	36	0.35[e]
2	**1a**	Bu^tCHO	-78°C/2 h[d]	-78→20°C/8 h	**3ab**	Bu^t	2,6-$Me_2C_6H_3$	Bu^tCHOH	63	0.37[f]
3	**1a**	PhCHO	-78°C/2 h[d]	-78→20°C/8 h	**3ad**	Bu^t	2,6-$Me_2C_6H_3$	PhCHOH	45	0.27[e]
4	**1a**	Et_2CO	-78°C/2 h[d]	-78→20°C/8 h	**3ae**	Bu^t	2,6-$Me_2C_6H_3$	Et_2COH	60	0.51[e]
5	**1a**	$(CH_2)_5CO$	-78°C/2 h[d]	-78→20°C/8 h	**3af**	Bu^t	2,6-$Me_2C_6H_3$	$(CH_2)_5COH$	50	0.42[e]
6	**1a**	EtOCOCl	-78°C/2 h[d]	-78→20°C/8 h	**3ag**	Bu^t	2,6-$Me_2C_6H_3$	EtOCO	52	0.60[e]
7	**1a**	n-$C_7H_{15}CONMeOMe$	-78°C/2 h[d]	-78→20°C/8 h	**3ai**	Bu^t	2,6-$Me_2C_6H_3$	n-$C_7H_{15}CO$	26	0.52[e]
8	**1b**	Pr^iCHO	-78°C/1 h	-78°C/1.5 h	**3ba**	Bu^t	n-C_8H_{17}	Pr^iCHOH	(32)[g]	0.32[f,h]
9	**1b**	Bu^tCHO	-78°C/1 h	-78°C/1.5 h	**3bb**	Bu^t	n-C_8H_{17}	Bu^tCHOH	(48)[g]	0.35[f,h]
10	**1b**	n-$C_5H_{11}CHO$	-78°C/1 h	-78°C/1.5 h	**3bc**	Bu^t	n-C_8H_{17}	n-$C_5H_{11}CHOH$	(61)[g]	0.38[f,h]
11	**1b**	PhCHO	-78°C/1 h	-78°C/1 h	**3be**	Bu^t	n-C_8H_{17}	PhCHOH	(43)[g]	0.28[f,h]
12	**1b**	EtOCOCl	-78°C/1 h	-78°C/2 h	**3bg**	Bu^t	n-C_8H_{17}	EtOCO	72	0.42[f]
13	**1c**	EtOCOCl	-78°C/2 h	-78→20°C/3 h	**3cg**	n-C_6H_{13}	2,6-$Me_2C_6H_3$	EtOCO	80	0.50[f]
14	**1d**	EtOCOCl	-78°C/2 h	-78→20°C/3 h	**3dg**	c-C_6H_{11}	2,6-$Me_2C_6H_3$	EtOCO	65	0.34[f]
15	**1d**	MeOCSCl	-78°C/2 h	-78°C/2 h	**3dh**	c-C_6H_{11}	2,6-$Me_2C_6H_3$	MeOCS	41	0.26[f]

[a] All products **3** (or **5**) were >94% pure (GLC and/or 300 MHz ^1H NMR) and were fully characterised by spectroscopic means (IR, ^1H and ^{13}C NMR, and MS). [b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) except otherwise stated, based on the starting material **1**. [c] Silica gel, hexane/ethyl acetate. [d] After the lithiation step the excess of lithium was removed by filtration at -78°C (see text). [e] Eluant ratio: 9/1. [f] Eluant tratio: 19/1. [g] Crude yield; this compound decomposes during the purification by column chromatography giving mainly the corresponding hydroxyketone **5**. [h] R_f value for the corresponding compound **5ba-bc,be**.

Table 2. Preparation of Compounds **4**

Entry	Starting material	Electrophile E^+	Reaction conditions		Product[a]		
			Lithiation	S_E	No.	Yield (%)[b]	R_f[c]
1	**1a**	$(CH_2)_5CO$	-78°C/1.5 h	-78→20°C/12 h	**4af**	46	0.30
2	**1a**	EtOCOCl	-78°C/2 h	-78°C/2 h	**4ag**	30	0.26
3	**1d**	Et_2CO	-78°C/3 h	-78°C/3 h	**4de**	42	0.22
4	**1d**	$(CH_2)_5CO$	-78°C/2 h	-78→20°C/2 h	**4df**	25	0.31

[a] Products **4** were >95% pure (GLC and/or 300 MHz ^1H NMR) and were fully characterised by spectroscopic means (IR, ^1H and ^{13}C NMR, and MS). [b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate). [c] Silica gel, hexane/ethyl acetate: 19/1.

In conclusion, we have described here a new and simple method to prepare imidoyllithium intermediates, by a naphthalene-catalysed chlorine-lithium exchange, which are adequate acyllithium synthetic equivalents.[12]

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