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Title: Magnesium Aldimines Prepared by Addition of Organomagnesium Halides to 2,4,6-Trichlorophenyl Isocyanide . Synthesis of 1,2-Dicarbonyl Derivatives.

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Magnesium Aldimines Prepared by Addition of Organomagnesium Halides to 2,4,6-Trichlorophenyl Isocyanide. Synthesis of 1,2-Dicarbonyl Derivatives

Kuno Schwärzer, Andreas Bellan, Maximilian Zöschg, Konstantin Karaghiosoff, and Paul Knochel*[a]

Dedicated to Armin de Meijere in celebration of his 80th birthday

Abstract: We report the selective addition of organomagnesium reagents to 2,4,6-trichlorophenyl isocyanide leading to magnesiated aldimines which react with *Weinreb* amides, ketones or carbonates to provide the corresponding carbonyl derivatives after acidic cleavage. This allows an efficient synthesis of 1,2-dicarbonyl compounds and α-hydroxy ketones.

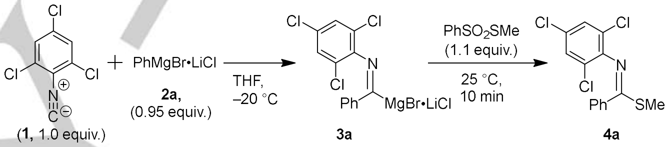
Isocyanides are widely used in heterocyclic synthesis.[1] These unsaturated compounds show carbenoic behaviour (Figure 1)[2] and Walborsky has shown in pioneer work that organometallics of lithium or magnesium added to tertiary or aryl isocyanides leading to metallo aldimines that were readily trapped with several classes of electrophiles.[3] Based on this reactivity several intramolecular ring closing reactions have been developed.[4]

Figure 1. Representation of an isocyanide as a linear carbene stabilized via delocalization of the nitrogen lone pair.[2]

Herein, we wish to report the selective addition of *Grignard* reagents to isocyanides. An optimization study showed that 2,4,6-trichlorophenyl isocyanide (**1**) was an excellent acceptor for arylmagnesium halide additions.[5] This is most likely due to the strong inductive electron-withdrawing effect of the chloride substituents which increases the carbenoic character of the isocyanide.[2] Thus, the reaction of phenylmagnesium halide (**2a**), prepared by the reaction of phenyl bromide with magnesium turnings in the presence of LiCl (0 °C to 25 °C, 15 h),[6] with the isocyanide **1** was performed in THF at −20 °C using various reaction times (Table 1, entries 1 – 4).

It was found that the addition was completed within 5 min at −20 °C providing the magnesiated aldimine **3a** which was trapped with $PhSO_2SMe$[7] (1.1 equiv., 25 °C, 10 min) leading to the thioimidate **4a** in almost quantitative yield (entry 2). Using a *Grignard* reagent prepared without LiCl resulted in a very low conversion (entry 3). In order to determine the *E*/*Z*-stereochemistry, we have prepared the crystalline thioimidate **4b** from *p*-dimethylaminophenylmagnesium bromide (**2b**) and determined its structure by X-ray analysis (Figure 2) showing that only *E*-**4b** was formed.[8]

Table 1. Condition screening for the reaction of 2,4,6-trichlorophenyl isocyanide **1** with the phenylmagnesium halide **2a**.



Entry	Time [min]	Yield [%][a]
1	2	60
2	5	97[b]
3	10	96 (6)[c]
4	20	82

[a] GC yields using undecane as internal standard. [b] Isolated yield of analytically pure product [c] Using a *Grignard* reagent prepared without LiCl.

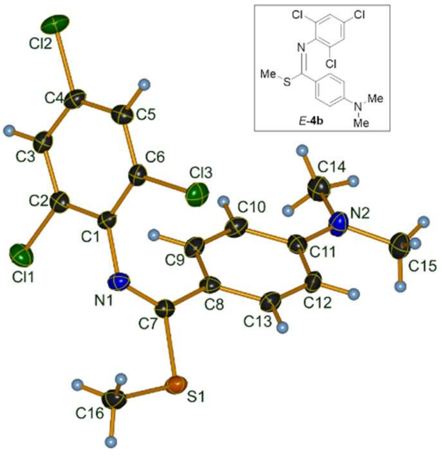


Figure 2. X-ray structure of the thioimidate **4b**, DIAMOND representation, thermal ellipsoids are drawn at 50% probability level.

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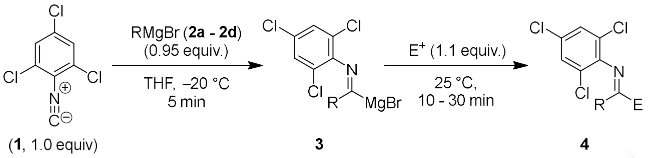
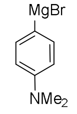
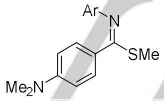
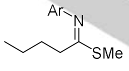
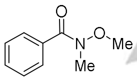
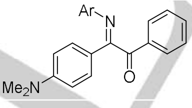
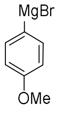
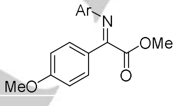
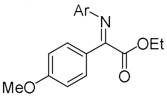
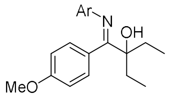
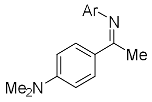
Thus, we have explored the scope of the reaction between the magnesiated aldimines **3** and various electrophiles. Both electron-rich arylmagnesium halides such as **2b** and an alkylmagnesium halide like *n*-butylmagnesium bromide complexed with LiCl (**2c**) added to the aryl isocyanide **1**. The resulting aldimines were successfully trapped with $PhSO_2SMe$ to afford the thioimidates **4b** and **4c** in 56 and 65% yield respectively (Table 2, entries 1 – 2). It should be noted, that electron-poor arylmagnesium halides bearing functional groups such as an ester or a nitrile, as well as arylmagnesium halides with substituents in *ortho* position did not add to the isocyanide **1** under various conditions. Nevertheless, we have found that magnesiated aldimines **3** reacted readily with various carbonyl derivatives such as the *Weinreb* amide **5a**,[9] dimethyl or diethyl carbonate and diethyl ketone leading to the expected products **4d** – **4g** in 59 – 91% yield (entries 3 – 6). The reaction with methyl iodide provided the imine **4h** in 35% yield (entry 7), while benzaldehyde did not react at all.

Table 2. Reaction of the isocyanide **1** with *Grignard* reagents followed by trapping of the formed magnesiated aldimines **3** with various electrophiles.

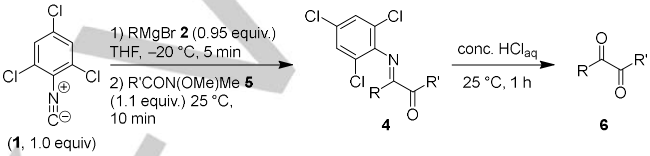


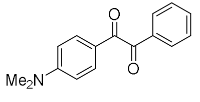
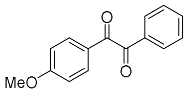
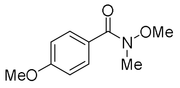
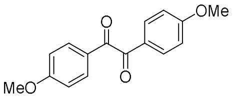
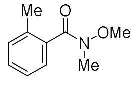
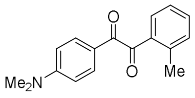
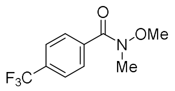
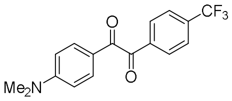
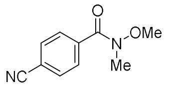
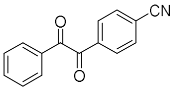
Entry	*Grignard* reagent **2**[a]	Electrophile E+	Product[b], [c]
1	 **2b**	$PhSO_2SMe$	 **4b**, 56%
2	*n*BuMgBr **2c**	$PhSO_2SMe$	 **4c**, 65%
3	**2b**	 **5a**	 **4d**, 91%
4	 **2d**	$(MeO)_2CO$	 **4e**, 66%
5	**2d**	$(EtO)_2CO$	 **4f**, 72%
6	**2d**	Et_2CO	 **4g**, 59%
7	**2b**	MeI	 **4h**, 35%

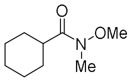
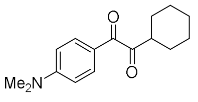
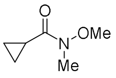
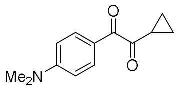
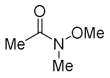
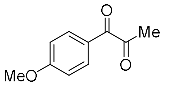
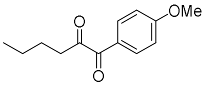
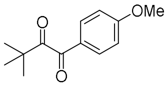
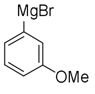
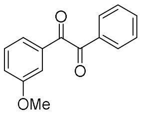
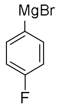
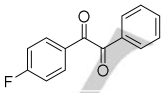
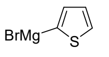
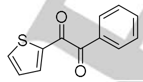
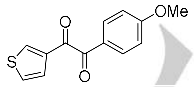
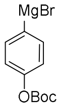
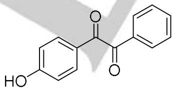
[a] Complexated LiCl omitted for clarity. [b] Ar = 2,4,6-trichlorophenyl. [c] Isolated yields of analytically pure products.

These preliminary results showed that the addition to *Weinreb* amides was especially efficient. Therefore, we have treated a range of magnesiated aldimines **3** with *Weinreb* amides followed by direct acidic cleavage of the imino function leading to 1,2-diketones of type **6** (Table 3).

Table 3. Reaction of magnesiated aldimines **3** with various *Weinreb* amides followed by acidic cleavage leading to 1,2-diketones **6**.



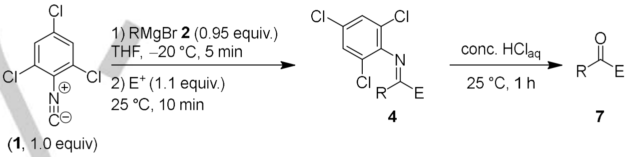
Entry	*Grignard* reagent **2**[a]	*Weinreb* amide **5**	Product[b]
1	**2b**	**5a**	 **6a**, 76%
2	**2d**	**5a**	 **6b**, 91%
3	**2d**	 **5b**	 **6c**, 76%
4	**2b**	 **5c**	 **6d**, 63%
5	**2b**	 **5d**	 **6e**, 59%
6	**2a**	 **5e**	 **6f**, 42%

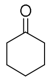
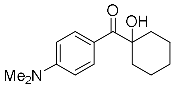
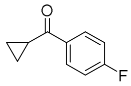
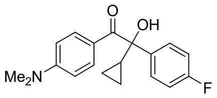
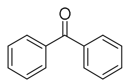
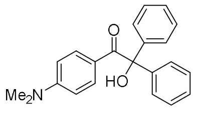
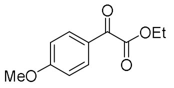
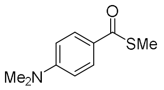
7	**2b**	 **5f**	 **6g**, 69%
8	**2b**	 **5g**	 **6h**, 69%
9	**2d**	 **5h**	 **6i**, 64%
10	**2c**	**5b**	 **6j**, 71%
11	*t*BuMgCl **2e**	**5b**	 **6k**, 48%
12	 **2f**	**5a**	 **6l**, 65%
13	 **2g**	**5a**	 **6m**, 82%
14	 **2h**	**5a**	 **6n**, 61%
15	 **2i**	**5b**	 **6o**, 38%
16	 **2j**[c]	**5a**	 **6p**, 68%[d]

[a] Complexated LiCl omitted for clarity. [b] Isolated yields of analytically pure products. [c] Formed via magnesium insertion at −10 °C over 1 h. [d] Stirred for 15 h with HCl to ensure cleavage of the Boc-group.

A one-pot reaction sequence consisting of the magnesium aldimine formation, subsequent trapping with the *Weinreb* amide **5a** and acidic cleavage of the imino function using concentrated aqueous HCl proceeded well with the electron-rich *Grignard* reagents **2b** and **2d**, providing the expected 1,2-diketones **6a** and **6b** in 76 and 91% yield respectively (entries 1 – 2). This reaction sequence tolerated electron-rich as well as electron-poor aryl-substituted *Weinreb* amides (entries 3 – 6). Furthermore, a range of various alkyl-substituted *Weinreb* amides (**5f** – **5h**) was successfully employed, yielding the corresponding 1,2-diketones **6g** – **6i** in 64 – 69% yield (entries 7 – 9). The scope of *Grignard* reagents was also further explored including *n*-butylmagnesium bromide (**2c**), *t*-butylmagnesium chloride (**2e**) as well as *meta*-anisylmagnesium bromide (**2f**) and *para*-fluorophenylmagnesium bromide (**2g**), which led to the respective 1,2-diketones **6j** – **6m** in 48 – 82% yields (entries 10 – 13). Heterocyclic *Grignard* reagents such as thiophen-2-ylmagnesium bromide (**2h**) and thiophen-3-ylmagnesium bromide (**2i**) underwent the addition to the isocyanide **1** leading to the 1,2-diketones **6n** and **6o** in 61% and 38% yield respectively (entries 14 – 15). In addition, the Boc-protected *para*-phenol *Grignard* reagent **2j**[10] provided the corresponding magnesiated aldimine which was trapped with the *Weinreb* amide **5a**. Subsequent treatment with concentrated aqueous HCl for 15 h led to a complete cleavage of both the imino function as well as the Boc protecting group providing the 1,2-diketone **6p** in 68% yield (entry 16).

Table 3. Reaction of magnesiated aldimines **3** with various electrophiles followed by acidic cleavage.



Entry	*Grignard* reagent **2**	Electrophile E$^+$	Product[a]
1	**2b**		 **7a**, 40%
2	**2b**		 **7b**, 58%
3	**2b**		 **7c**, 55%
4	**2d**	$(EtO)_2CO$	 **7d**, 58%[b]
5	**2b**	$PhSO_2SMe$	 **7e**, 67%

[a] Isolated yields of analytically pure products. [b] 3 M HCl was used instead of conc. HCl.

Finally, we extended the one-pot procedure to reactions with various other electrophiles (Table 3). Thus, by using alkyl and aryl ketones, we have achieved the formation of the α-hydroxy ketones **7a** – **7c** in 40 – 58% yield (entries 1 – 3). In the case of diethyl carbonate the cleavage of the imino function was achieved using 3 M aqueous HCl in order to avoid the decomposition of resulting α-keto ester **7d** (entry 4). The cleavage of the imino bond in the thioimidate **4b** required concentrated aqueous HCl, leading to the formation of the thioester **7e** in 67% yield (entry 5).

In summary, we have reported an efficient addition of organomagnesium halides to 2,4,6-trichlorophenyl isocyanide (**1**). This isocyanide gave much better results than related aryl isocyanides.[5] Quenching reactions with *Weinreb* amides as well as ketones provided the desired functionalized carbonyl derivatives (1,2-diketones of type **6** and α-hydroxy ketones **7a** – **7c**). Further extensions of this method are underway.

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Keywords: Organomagnesium halides • Isocyanides • Magnesium aldimines • Weinreb amides• 1,2-Diketones

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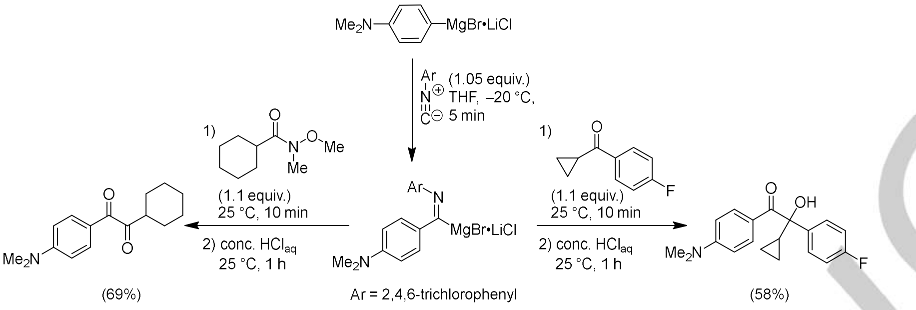
COMMUNICATION



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Magnesium Aldimines Prepared by Addition of Organomagnesium Halides to 2,4,6-Trichlorophenyl Isocyanide. Synthesis of 1,2-Dicarbonyl Derivatives.

A selective addition of organomagnesium halides to 2,4,6-trichlorophenyl isocyanide leads to magnesium aldimines. Subsequent trapping with *Weinreb* amides or ketones and acidic cleavage gives access to functionalized 1,2-diketones or α-hydroxy ketones (see Figure).