

Reaction of magnesium carbenoids with *N*-lithio arylamines: a novel method for generation of non-stabilized α -amino-substituted carbanions and a new synthesis of α -amino acid derivatives

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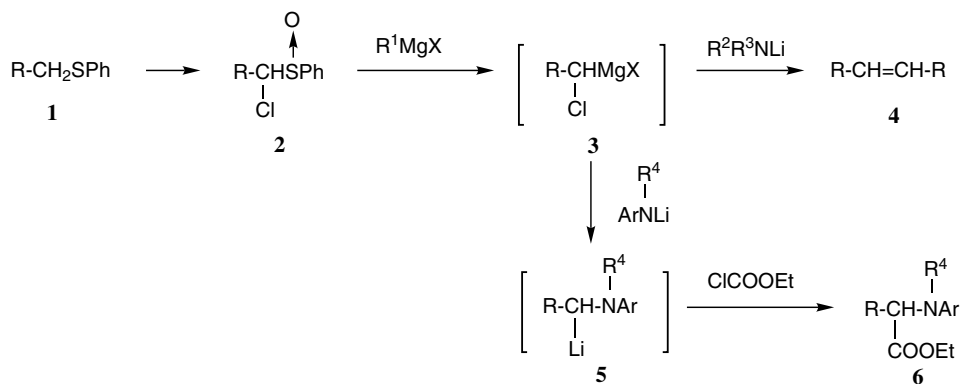
Abstract—Treatment of 1-chloroalkyl phenyl sulfoxides with a Grignard reagent at low temperature afforded magnesium carbenoids in quantitative yields. The magnesium carbenoids were found to be reactive with *N*-lithio alkylamines and *N*-lithio arylamines. The reaction with *N*-lithio alkylamines afforded an olefin, which was derived from dimerization of the magnesium carbenoid, in moderate yield. The reaction with *N*-lithio arylamines gave the adducts, α -amino-substituted carbanions, in good yields. From these intermediates, a novel synthesis of α -amino acid derivatives and *N,N*-dialkyl arylamines having a deuterium at the α -position was realized. © 2004 Published by Elsevier Ltd.

Carbenes and carbenoids have been well known as a highly reactive carbon species and are recognized as useful intermediates in organic synthesis.¹ Generation of carbenes and carbenoids has mainly been carried out in two ways: (a) photolysis, pyrolysis, and metal-catalyzed decomposition of diazo compounds,² (b) base-induced α -elimination.^{1,3}

In this decade, we have been interested in the generation of magnesium carbenoids from α -halo sulfoxides via sulfoxide–magnesium exchange reaction⁴ and applica-

tions of the generated magnesium carbenoids to new methods for organic synthesis.⁵ In continuation of our investigation of the chemistry of the magnesium carbenoids, we recently studied the generation of simple magnesium carbenoids **3** from 1-chloroalkyl phenyl sulfoxides **2** with Grignard reagents and reaction of **3** with nitrogen nucleophiles (Scheme 1).

Interestingly, the reaction of the magnesium carbenoid **3** with *N*-lithio dialkylamine gave no aminated product but dimeric product **4**. In sharp contrast to this result,



Scheme 1.

Keywords: Sulfoxide–magnesium exchange; Magnesium carbenoid; Dimerization; α -Amino-substituted carbanion; α -Amino acid.

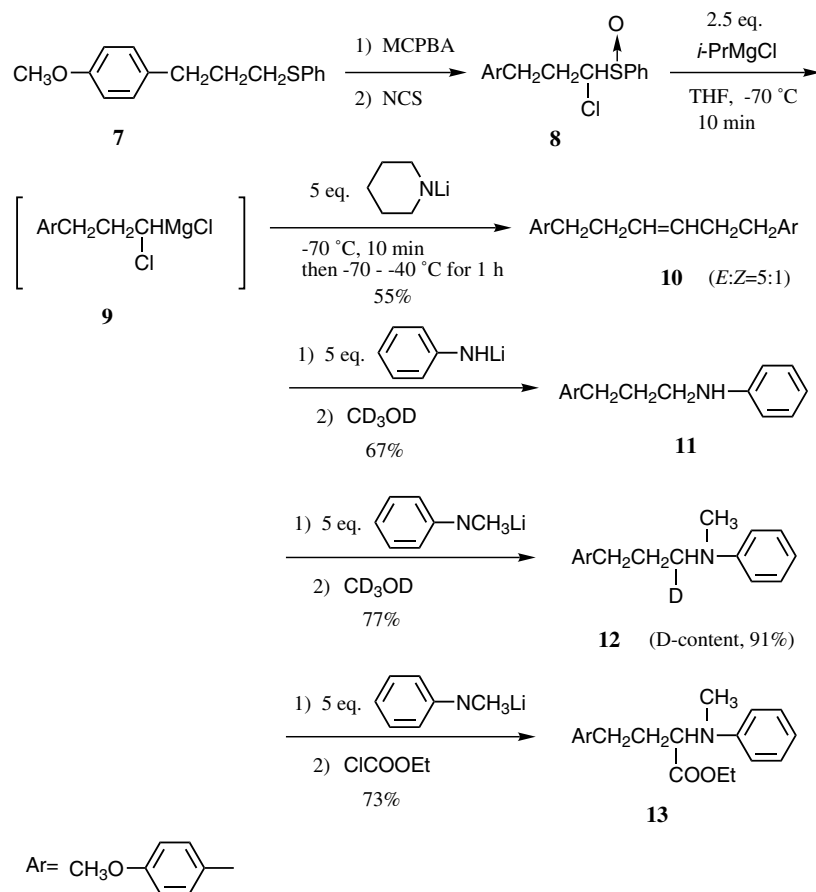
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the reaction of **3** with several *N*-lithio arylamines afforded the adduct, α -amino-substituted carbanions **5**. From the adduct **5**, a novel synthesis of α -amino acid derivatives **6** was realized (Scheme 1).

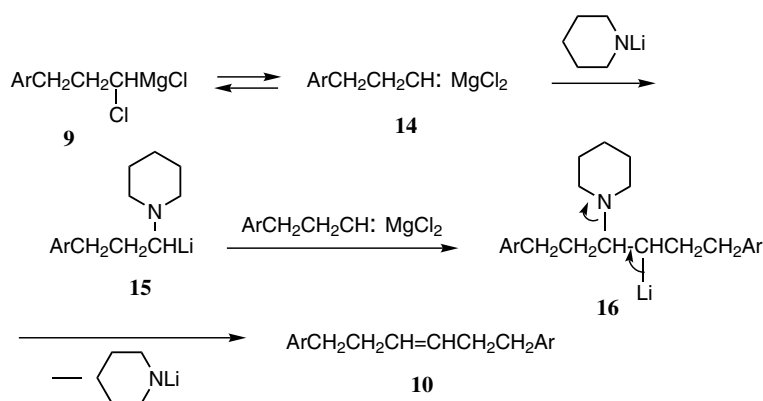
The representative reactions are reported by using 1-chloroalkyl phenyl sulfoxide **8**, derived from sulfide **7** in high overall yield,⁶ as an example (Scheme 2). Treatment of **8** in THF with 2.5 equiv of *i*-PrMgCl at -70°C cleanly gave the magnesium carbenoid **9** in a quantitative yield.⁶ To this solution was added 5 equiv of *N*-lithio

piperidine through a canula and the temperature of the reaction mixture was allowed to warm to -40°C for 1 h. We obtained an olefin **10** (dimer of the carbenoid **9**) in 55% yield. Quite interestingly, this olefin **10** was not obtained at all from the carbenoid **9** in the absence of *N*-lithio piperidine. Obviously, *N*-lithio piperidine is essential in this olefin formation.

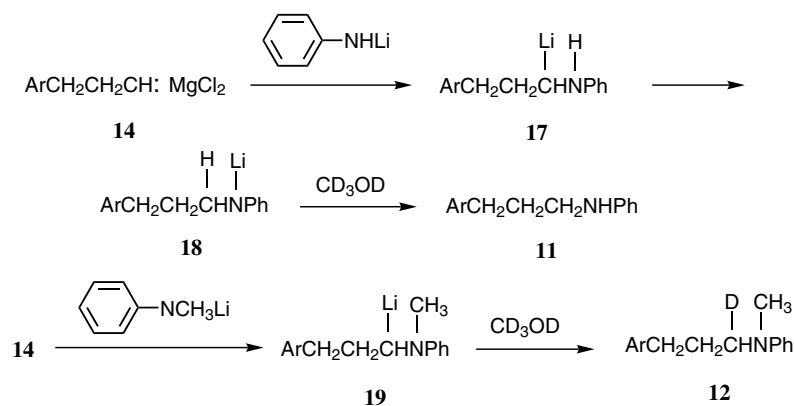
A plausible mechanism for the formation of the olefin **10** is proposed as shown in Scheme 3. Thus, the magnesium carbenoid **9** (or **14**) reacted with *N*-lithio piperidine to



Scheme 2.

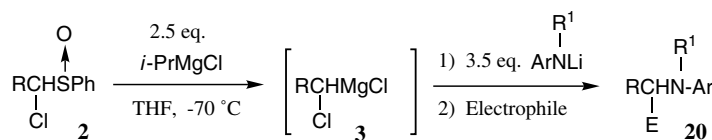


Scheme 3. A plausible mechanism for the formation of the dimer **10**.



Scheme 4. A plausible mechanism for the formation of the *N*-alkylaniline **11** and *N*-(1-deuterated alkyl)-*N*-methylaniline **12** by the reaction of the magnesium carbenoid **14** with *N*-lithio aniline and *N*-lithio *N*-methylaniline.

Table 1. Synthesis of *N,N*-dialkyl arylamine and α -amino acid derivatives **20** from the magnesium carbenoid **3** by the reaction of *N*-lithio arylamine followed by electrophiles



Entry	2 R	Ar	R ¹	Electrophile	E	20 Yield/%
1	CH ₃ O-C ₆ H ₄ -CH ₂ CH ₂	CH ₃ O-C ₆ H ₄ -	CH ₃	CD ₃ OD	D	81% ^a
2	CH ₃ O-C ₆ H ₄ -CH ₂ CH ₂	CH ₃ O-C ₆ H ₄ -	CH ₃	ClCOOEt	COOEt	74%
3	CH ₃ O-C ₆ H ₄ -CH ₂ CH ₂	Cl-C ₆ H ₄ -	CH ₃	CD ₃ OD	D	79% ^a
4	CH ₃ O-C ₆ H ₄ -CH ₂ CH ₂	Cl-C ₆ H ₄ -	CH ₃	ClCOOEt	COOEt	73%
5	CH ₃ O-C ₆ H ₄ -CH ₂ CH ₂	CH ₃ O-C ₆ H ₄ -	PhCH ₂	CD ₃ OD	D	69% ^b
6	CH ₃ O-C ₆ H ₄ -CH ₂ CH ₂	CH ₃ O-C ₆ H ₄ -	PhCH ₂	ClCOOEt	COOEt	67%
7	C ₆ H ₅ -CH ₂ CH ₂	CH ₃ O-C ₆ H ₄ -	PhCH ₂	CD ₃ OD	D	73% ^c
8	C ₆ H ₅ -CH ₂ CH ₂	CH ₃ O-C ₆ H ₄ -	PhCH ₂	ClCOOEt	COOEt	71%
9	Cyclohexyl-CH ₂	CH ₃ O-C ₆ H ₄ -	CH ₃	CD ₃ OD	D	70% ^b
10	Cyclohexyl-CH ₂	CH ₃ O-C ₆ H ₄ -	CH ₃	ClCOOEt	COOEt	68%
11	Cyclohexyl-CH ₂	Cl-C ₆ H ₄ -	CH ₃	CD ₃ OD	D	72% ^c
12	Cyclohexyl-CH ₂	Cl-C ₆ H ₄ -	CH ₃	ClCOOEt	COOEt	68%
13	Cyclohexyl-	CH ₃ O-C ₆ H ₄ -	CH ₃	CD ₃ OD	D	48% ^d
14	Cyclohexyl-	CH ₃ O-C ₆ H ₄ -	CH ₃	ClCOOEt	COOEt	48%
15	Cyclohexyl-	Cl-C ₆ H ₄ -	CH ₃	CD ₃ OD	D	42% ^b
16	Cyclohexyl-	Cl-C ₆ H ₄ -	CH ₃	ClCOOEt	COOEt	41%

^a D-content 90%.

^b D-content 97%.

^c D-content 95%.

^d D-content 99%.

give the adduct **15**, which reacted again with the carbenoid to give **16**. β -Elimination of *N*-lithio piperidine from **16** afforded the olefin **10**.

In contrast to the reaction of **9** with *N*-lithio piperidine, the reaction with *N*-lithio aniline gave *N*-alkylaniline **11** in good yield (Scheme 2). This reaction was quenched with excess CD₃OD; however, no deuterium was incorporated in the *N*-alkylaniline **11**. Next, the magnesium carbenoid **9** was treated with 5 equiv of *N*-lithio *N*-methylaniline under the same conditions as above, and the reaction was quenched with excess CD₃OD. We obtained the *N,N*-dialkylaniline **12** in 73% yield and the product was deuterated on the α -carbon. The plausible mechanism of this interesting reaction is shown in Scheme 4.

The reaction of the magnesium carbenoid with *N*-lithio aniline gave the adduct, *N*-alkylaniline having carbanion at the α -position **17**. The adduct has an acidic hydrogen on the nitrogen, and the carbanion quickly picks up this acidic hydrogen to give **18**. So, as described above, on quenching this reaction with CD₃OD no deuterium was incorporated on the α -carbon. In contrast to this, the reaction with *N*-lithio *N*-methylaniline provided the adduct **19**, which has no acidic hydrogen, to give the product having the alkyl group deuterated at the α -position **12**. Generation of the α -amino-substituted carbanions is well recognized to be quite difficult from unactivated amines.⁷ The results obtained in this study are highly notable as a new method for generation of non-stabilized α -amino carbanions.⁸

In order to synthesize α -amino acid derivatives, we tried to trap this carbanion **19** with ethyl chloroformate and, fortunately, the expected reaction worked to afford the α -amino acid derivative **13** in 73% yield (see Scheme 2).⁹ Generality of this reaction was investigated using four kinds of 1-chloroalkyl phenyl sulfoxides **2** and *N*-methyl *p*-anisidine, *N*-benzyl *p*-anisidine, and *N*-methyl *p*-chloroaniline. The results are summarized in Table 1.

Entries 1–6 show that the reaction of the magnesium carbenoid **9** with three kinds of arylamines, *N*-methyl *p*-anisidine, *N*-methyl *p*-chloroaniline, and *N*-benzyl *p*-anisidine, gave equally good yields (67–74%) of the α -amino acid derivatives. The reaction starting from the sulfoxide having a 2-phenylethyl group as R gave similar results (entries 7 and 8). Entries 9–12 show the reaction starting from the sulfoxide **2** having a cyclohexylmethyl group as R. The results were shown to be almost equal to those described above. Interestingly, the reaction starting from the sulfoxide having a cyclohexyl group as R showed markedly diminished yield of the α -amino acid derivatives (entries 13–16). Steric hindrance is thought to be the reason for the lowering of the yield, at present.

In conclusion, we have found a novel and versatile method for the formation of non-stabilized α -amino-substituted carbanions by the reaction of the magnesium carbenoid and *N*-lithio *N*-alkylarylamines. Investigation of the scope and limitation, and development of this

reaction to an asymmetric synthesis of α -amino acid derivatives is underway in these laboratories.

Acknowledgements

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9. To a solution of *i*-PrMgCl (0.5 mmol) in THF (0.5 mL) at -70°C was added a solution of **8** (62 mg; 0.2 mmol) in 0.4 mL of THF dropwise with stirring. After 10 min, a solution of *N*-lithio *N*-methylaniline (prepared from *N*-methylaniline (1 mmol) and *n*-BuLi (1.2 mmol) in 2 mL of THF at 0°C) was added to a solution of the magnesium carbenoid **9** through a cannula and the reaction mixture was slowly allowed to warm to -40°C for 1 h. Ethyl

chloroformate (1 mmol) was added to the reaction mixture dropwise with stirring and the solution was stirred at -40°C for 20 min. The reaction was quenched by adding H_2O . The whole mixture was extracted with CHCl_3 and the product was purified by silica gel column chromatography to give **13** (48 mg; 73%) as a colorless oil. IR (neat) 2955, 1731 (CO), 1599, 1512, 1300, 1247, 1035cm^{-1} ; $^1\text{H NMR}$ δ 1.20 (3H, t, $J = 7.0$ Hz), 2.11–2.18 (1H, m), 2.20–2.28 (1H, m), 2.53–2.59 (1H, m), 2.63–2.70 (1H, m), 2.93 (3H, s), 3.78 (3H, s), 4.13 (2H, m), 4.31 (1H, dd, $J = 9.3, 5.5$ Hz), 6.75 (3H, m), 6.80 (2H, d, $J = 8.6$ Hz), 7.05 (2H, d, $J = 8.6$ Hz), 7.22 (2H, t, $J = 8.3$ Hz). MS m/z (%) 327 (M^+ , 15), 254 (75), 121 (100). Calcd for $\text{C}_{20}\text{H}_{25}\text{O}_3\text{N}$: M, 327.1838. Found: m/z 327.1835.