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Published in:
Synthesis-Stuttgart

DOI:
[10.1055/s-1988-27507](https://doi.org/10.1055/s-1988-27507)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
1988

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

FERINGA, BL., JANSEN, JFGA., & Jansen, J. F. G. A. (1988). A NEW SYNTHESIS OF IMINES VIA GRIGNARD AND CUPRATE ADDITIONS TO N-TRIMETHYLSILYLFORMAMIDES. *Synthesis-Stuttgart*, 1988(3), 184-186. <https://doi.org/10.1055/s-1988-27507>

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A New Synthesis of Imines via Grignard- and Cuprate Additions to *N*-Trimethylsilylformamides

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Various imines and some amines were synthesized by the addition of Grignard reagents, homo- and hetero-cuprates to *N*-silylated-, *N*-alkyl- or *N*-arylformamides **1**.

The addition reaction of organolithium and organomagnesium reagents to *N,N*-disubstituted amides is a facile method for the synthesis of aldehydes and ketones.^{1–6} Especially *N*-methyl-*N*-formylaminopyridine² and *N*-formylpiperidine⁶ were shown to formylate efficiently a wide variety of Grignard reagents. We recently described that the reaction of aryllithium compounds with *N*-trimethylsilyl-*N*-alkyl- or *N*-arylformamides yields imines.⁷ We now wish to report the formation of imines from the reaction of *N*-trimethylsilyl-*N*-alkyl- or *N*-arylformamides **1**, with Grignard reagents (Scheme A), and Homo- and Hetero-cuprates (Scheme B). Thus the reaction of *N*-trimethylsilyl-*N*-phenylformamide with 1.3 equivalents of isopropylmagnesium bromide at -80°C in tetrahydrofuran gave imine **2** (R^1 = isopropyl, R^2 = phenyl) in 94 % yield. The result of the

new imine synthesis using various Grignard reagents and homo- and hetero-cuprates are summarized in Tables 1 and 2, respectively.⁸ Good to high yields of pure imines are obtained after distillation. ^1H - and ^{13}C -NMR data for all aldimines formed, show that only one isomer with *E*-configuration is present. The imines **2** were conveniently converted into secondary amines **3** when reduced with lithium aluminum hydride (Table 1). Our results constitute a new general method for the synthesis of aldimines as well as secondary amines upon reduction.

Table 1. Imines **2** from the Addition of Grignard Reagents to *N*-Silylated Formamides and Amines **3** via LiAlH_4 Reduction of **2**

Product	Yield ^a (%)	mp ($^{\circ}\text{C}$) or bp ($^{\circ}\text{C}$)/mbar	Molecular Formula or Lit. mp ($^{\circ}\text{C}$) or bp ($^{\circ}\text{C}$)/mbar
2a	97	51–52	52 ¹⁵
2b	69	120–121/15	— ^{8,b}
2c	94	48–49/1.3	95/24
2d	90	70–71/1.1	— ^{8,17,b}
2e	— ^b	—	$\text{C}_{10}\text{H}_{11}\text{N}$ (145.2) ^c
2f	30	191	— ^{8,b}
2g	81	70–72/16	72–73/17 ¹⁸
2h	83	120–122/23	112–113/19 ¹⁹
2i	94	124–126/0.3	116–117/0.13 ²⁰
3a	96	110–111/0.7	201–203/49 ²¹
3b	71	122–124/12	138–140/25 ²²
3c	81	88–90/3	111.5–113.5/15 ²³
3d	77	72–74/3	98.5–100/15 ²⁴
3e	93	76–77/1	116–122/23 ²⁵
3f	60	114–116	116–118 ²⁶
3g	80	72–74/16	77–78/23 ²⁷
3h	79	64–67/0.3	50–55/0.13 ²⁸
3i	94	100–101/0.4	175–180/20 ²⁹

^a Isolated yield.

^b No bp reported.

^c Crude yield: > 95 %. Pure product could not be isolated due to fast polymerization on distillation or during chromatography.

Scheme A

Table 2. Imines **2** and Amines **4** via the Addition of Organocuprates to **1**

Product	R ¹	R ²	Method	Yield (%)	bp ($^{\circ}\text{C}$)/mbar	Molecular Formula ^a or Lit. bp ($^{\circ}\text{C}$)/mbar
2j	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	A	92 ^b	88–89/27	C ₉ H ₁₉ N (141.3)
2k	<i>n</i> -C ₄ H ₉	C ₆ H ₅ CH ₂	B	76	88–90/0.07	C ₁₂ H ₁₇ N (175.3)
4a	C ₂ H ₅	—	A	60	68–69/0.4	114/19 ³⁰
4b	<i>n</i> -C ₄ H ₉	—	B	30	110–111/1.5	112–113/1.6 ³¹
			— ^c	74		
			— ^c	75		
4c	<i>n</i> -C ₁₂ H ₂₅	—	A	65	> 250/0.013	C ₃₁ H ₅₇ N (443.8)
			B	63		

^a See Table 3 for HRMS.

^b Reduction of **2j** with LiAlH_4 gave *N*-butyl-*N*-pentyl amine in 68 % yield.

^c Using 2.6 equiv. of *n*-BuLi and 0.02 equiv. of CuBr with a reaction time of 24 h.

The products of the reaction of **1** with homo- and heterocuprates⁹ depend on the substituent R^2 (Scheme B). In contrast with the formation of imines from *N*-trimethylsilyl-*N*-alkyl-substituted formamides, it was found that the cuprate addition to *N*-trimethylsilyl-*N*-aryl-substituted formamides results in the formation of α,α -disubstituted-*N*-arylamines **4** (Table 2).

Scheme B

It is conceivable that the formation of imines **2** and amines **4** takes place via addition of the organometallic reagent to *N*-trimethylsilylformamide **1** to provide intermediate **6** (Scheme C). Alternatively intermediate **7** can be formed either via

Scheme C

addition to **5** (in equilibrium with **1**)¹⁰ or via *N*- to *O*-shift of the trimethylsilyl group in intermediate **6**. The isolation of an α,β -unsaturated aldimine (product **2e**) shows that imine formation from these intermediates takes place during aqueous work-up, as α,β -unsaturated aldimines generally undergo rapid polymerization in the presence of Grignard reagents.¹¹ The absence of amines **4** when Grignard or organolithium reagents are used, even in excess, provides additional evidence that imines are *not* formed prior to work-up. Because only a catalytic amount of cuprous bromide is sufficient for the formation of amines **4** (product **2b** and **4b**), when R^2 is aryl, we propose that the combined effect of a Cu^+ counterion and a *N*-aryl-substituent causes the elimination of copper(I) trimethylsilanoate presumably from intermediate **7**. Subsequent alkylation of the imine **2** obtained in this way results in the formation of amines **4**.¹²

Summarizing the results from Tables 1 and 2 it is shown that aldimines and the corresponding amines can be synthesized in good yields from alkyl and aryl-Grignard reagents. Furthermore, they can be obtained from aryllithium compounds⁷ and from alkyllithium compounds via the organocopper reagent. The latter reaction has not been extensively studied yet. The synthesis of α,α -disubstituted-amines was successful only for *N*-trimethylsilyl-*N*-arylformamides so far.

All compounds were characterized by IR, ¹H-, ¹³C-NMR and MS data. For compound **2e**, only IR and ¹H-NMR data of the crude product were obtained due to its sensitive nature. The spectroscopic data for all new compounds are summarized in Table 3.

All reactions were carried out in dried glassware under a nitrogen atmosphere. THF was distilled over sodium (benzophenone) under nitrogen. The trimethylsilylformamides were prepared according to literature^{13,14} and used *in situ*. IR spectra were recorded on a P-Unicam Sp-200; ¹H- and ¹³C-NMR spectra were recorded on Hitachi Perkin Elmer R24B and Nicolet NT-200 spectrometers. Mass spectra were obtained on an AEI MS-902 spectrometer.

N-(2-Methylpropylidene)aniline (**2c**); Typical Procedure:

To a stirred solution of *N*-trimethylsilyl-*N*-phenylformamide (1.65 g, 10 mmol) in THF (50 mL) at $-80^\circ C$ is added a 2 N solution of isopropylmagnesium bromide in THF (6.5 mL, 13 mmol). Subsequently the temperature of the mixture is raised to room temperature over a period of 3.5 h. The mixture is poured into water (150 mL) followed by extraction with ether (3×50 mL). The organic solution is dried (Na_2SO_4). The solvent is evaporated and the crude liquid product **2c** distilled under reduced pressure; yield: 1.34 g (94%); bp $48-49^\circ C/1.3$ mbar (Lit.¹⁰ bp $95^\circ C/24$ mbar).

Table 3. Spectroscopic Data of New Compounds

Product	IR (neat) ν (cm ⁻¹)	¹ H-NMR (CDCl ₃ /TMS) δ , J (Hz)	¹³ C-NMR (CDCl ₃) δ	HRMS (m/z , M ⁺) calc. found	
2e	1600–1510 (C=C), 760–690 (C–H _{arom})	2.0 (s, 3H); 5.4 (m, 1H); 5.6 (m, 1H); 7.4–6.5 (m, 5H); 8.0 (s, 1H)	–	–	–
2j	1640 (C=N)	0.7–1.9 (m, 14H); 2.1–2.5 (m, 2H); 2.3 (t, 2H, J = 6); 7.6 (t, 1H, J = 5)	13.38 (q), 13.67 (q), 20.12 (t), 22.20 (t), 28.11 (t), 32.68 (t), 35.32 (t), 60.86 (t), 164.80 (d)	141.152	141.152
2k	1640 (C=N), 740–690 (C–H _{arom})	0.7–1.9 (m, 7H); 2.1–2.5 (m, 2H); 4.7 (s, 2H); 7.2 (s, 5H); 7.7 (t, 1H, J = 5)	13.52 (q), 22.03 (t), 27.66 (t), 35.24 (t), 64.61 (t), 126.51 (d), 127.47 (d), 128.06 (d), 138.46 (s), 165.97 (d)	175.136	175.137
4c	3400 (NH), 740–690 (C–H _{arom})	0.8–1.0 (m, 6H); 1.7 (br s, 44H); 3.3–3.5 (m, 2H); 6.4–7.3 (m, 5H)	14.02 (q), 22.61 (t), 25.81 (t), 28.67 (t), 29.28 (t), 29.56 (t), 30.07 (t), 30.24 (t), 30.52 (t), 31.35 (t), 31.84 (t), 34.82 (t), 52.76 (d), 112.72 (d), 120.65 (d), 128.80 (d), 129.13 (s)	443.449	443.448

***N*-(*sec*-Butyl)aniline (3c); Typical Procedure**

The above procedure with the same amount of starting materials is followed, but the ether solution, after drying, is added to a solution of LiAlH_4 (1.50 g, 40 mmol) in THF (50 mL). The mixture is stirred at reflux for 16 h. A shorter reflux period might be sufficient in some cases. After cooling of the solution to room temperature 10 % aqueous KOH (5 mL) is added. The mixture is stirred at reflux for 1 h, before being cooled to room temperature and filtered with suction. Omitting this KOH treatment results in 10 to 15 % lower yields. The salt residues are extracted with ether (100 mL) under reflux for 1 h. This procedure is repeated four times. The combined ether solutions are dried (MgSO_4), the solvent is evaporated and the resulting oily residue distilled to give **3c**; yield: 1.21 g (81 %); bp 88–90°C/3 mbar (Lit¹⁷ bp 111.5–113.5°C/15 mbar).

Preparation of *N*-Butyl-homocuprate; Typical Procedure:

To a stirred solution of CuBr (1.86 g, 13 mmol) in THF (80 mL) at –80°C is added a 1.6 N hexane solution of *n*-BuLi (41.6 mL, 26 mmol). This mixture is stirred for 1 h at –60°C and then used as such.

***N*-(5-Nonyl)aniline (4b); Typical Procedures:**

Method A: *N*-trimethylsilyl-*N*-phenylformamide (1.65 g, 10 mmol) dissolved in THF (50 mL) is added at –80°C to a solution of bis(*n*-butyl)lithiumcuprate (120 mL) in THF, hexane prepared as above. The mixture is allowed to warm slowly to room temperature (2.5 up to 3 h). A work-up as described for compound **2c** is followed by distillation to provide **4b** as an oil; yield: 2.10 g (96%); bp 110–111°C/1.5 mbar (Lit²⁵ bp 112–113°C/1.6 mbar).

Method B: To a stirred solution of *N*-trimethylsilyl-*N*-phenylformamide (1.65 g, 10 mmol) at –80°C is added CuBr (0.04 g, 0.02 equiv) followed by a 1.9 N solution of *n*-C₄H₉MgBr (13.5 mL) in THF (13.5 mL). Following the procedure described for Method A, **4b** is obtained pure on distillation; yield: 1.62 g (74 %).

Received: 16 February 1987; revised: 21 September 1987

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