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Zinc metal-promoted nucleophilic addition of nonactivated alkyl iodides to aromatic aldimines in the presence of chlorotrimethylsilane in ethyl acetate–DMI

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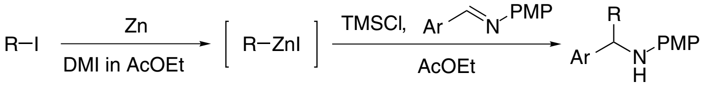
Dedicated to Prof. N. Sonoda on the occasion of his 70th birthday

Abstract—A variety of aromatic aldimines react with nonactivated alkyl iodides in the presence of zinc powder and a catalytic amount of chlorotrimethylsilane (TMSCl) in ethyl acetate–DMI to afford the corresponding α-alkylbenzylamine derivatives in good to excellent yields.

Organozinc reagents are very useful and versatile reagents for a variety of transformations in organic synthesis,[1] because of their high functional group compatibility. The Reformatsky[2] and the Barbier reactions of activated organic halides such as α-halo esters and allyl halides have been widely studied. However, alkylzinc reagents prepared from nonactivated halides are generally unreactive towards carbon nucleophiles due to their low nucleophilicity. Thus, these reactions usually require the aid of other metals or additives.[1,3] Several methods have been reported[1,4–8] for these purposes, such as the use of a Zn–Cu couple[5] or Rieke zinc[6] and the electro reduction of a zinc salt.[7] However, the synthetic utility of these methods may be considerably limited because special equipment, expensive reagents and multi-step procedures are required. Recently, we have reported that metallic zinc with TMSCl markedly promotes the reaction of halides with aldehydes and ketones to provide the corresponding olefins and alcohols.[9]

Nucleophilic addition of aromatic aldimines with organozinc reagents seems one of the most useful and efficient methods to synthesize benzylamine derivatives. Especially, the addition of organometallic reagents to the C=N bonds of imines and imine derivatives is a well-known process. Numerous studies have been reported,[10] for example, reactions with organozinc reagents such as diorganozinc[10a–c,e,11] and triorganozincates.[12] However, the addition of nonactivated alkylzinc halides to imines has been scarcely reported.[13] In this letter, we wish to report a mild, efficient and convenient zinc-promoted alkylation reaction of aldimines with nonactivated halides in the presence of additives (TMSCl and DMI) to provide the corresponding α-alkylbenzylamines in good to excellent yields (Scheme 1). To our knowledge,



Scheme 1.

Keywords: Amines; Imines; Nucleophilic addition; TMSCl; Zinc.

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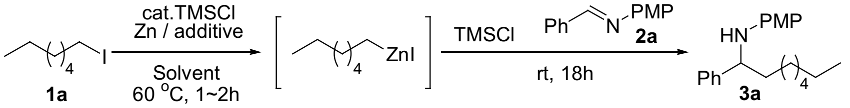
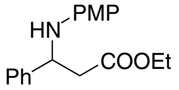
Table 1. Reaction of *n*-heptyl iodide (**1a**) with imine **2a**



Entry	Additive (equiv)	Solvent	TMSCl (equiv)	Yield (%)[a]
1	NMP (2.0)	THF	3.0	42
2	NMP (2.0)	Toluene	3.0	63
3	NMP (2.0)	CH_3CN	3.0	71
4	NMP (2.0)	AcOEt	3.0	70
5	NMP (2.0)	AcOEt	—	21
6	—	AcOEt	3.0	48[b]
7	DMI (2.0)	AcOEt	3.0	73
8	DMI (2.0)	AcOEt	1.5	72

[a] GCyield.

[b] Adduct of **2a** and AcOEt, ethyl 3-(*N*-PMP)-amino-3-phenylpropionate (**4**), was isolated in 42% as a by-product.



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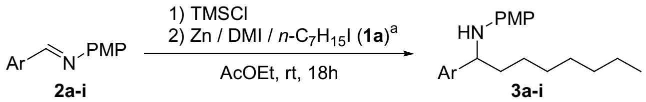
nucleophilic addition of nonactivated alkyl halides to aromatic aldimines using zinc metal has not yet been reported.

Organozinc reagents were usually prepared at 60 °C for 1–2 h in a solvent containing powdered metallic zinc (4.6 mmol), *n*-heptyl iodide (**1a**) (4.5 mmol) and a catalytic amount of TMSCl (0.14 mmol) in the presence of additives, and then TMSCl (9.0 mmol) and a solution of benzaldehyde *N*-(*p*-methoxyphenyl) imine (*N*-PMP imine) **2a** (3.0 mmol) in AcOEt (2.0 mL) was added at room temperature to the reaction mixture. Commercially available zinc powder (purity; 99.9%) were used without any pre-treatment. Detailed studies on the reaction of **1a** with **2a** to α-alkylbenzylamine derivative **3a** showed that this addition reaction is considerably influenced by the additives and the solvent as shown in Table 1.

The reaction of **1a** with **2a** smoothly took place in the presence of additives and a catalytic amount of TMSCl. Especially, 1,3-dimethyl-2-imidazolidinone (DMI) and *N*-methyl-2-pyrrolidone (NMP) as additives showed high reactivity and alkylzinc reagents were generated in situ. Though **3a** was obtained in the absence of additives and TMSCl, the reaction proceeded more smoothly and efficiently by the addition of NMP or DMI and TMSCl. As shown in Table 1, the best result for formation of **3a** was obtained when DMI and TMSCl were used in 2.0 and 3.0 equiv, respectively. AcOEt was found to be a much better solvent[14] for this reaction than other aprotic solvents.

To demonstrate the generality and efficiency of this reaction, we applied this combination system to a variety of aryl aldimines **2a**–**i**. Under the optimized conditions,[15] *n*-heptyl iodide (**1a**) was treated with a variety of imines **2a**–**i** in the presence of zinc powder to produce amines **3a**–**i** in good to excellent yields (Table 2). The yields of amines **3a**–**i** for the reaction were slightly dependent on the substituents on the aromatic ring. That is, the aryl aldimines with electron-withdrawing groups such as cyano and chloro gave the corresponding amines **3** in higher yields compared with those with electron-donating groups. Hetero aromatic aldimines also smoothly reacted (entries 7–9).

Table 2. The zinc-promoted reactions of *n*-heptyl iodide (**1a**) with aldimines **2**



Entry	Imine	Ar	Product (yield, %)[b]
1	**2a**	Ph	**3a** (70)
2	**2b**	*p*-Me–C_6H_4	**3b** (64)[c]
3	**2c**	*p*-MeO–C_6H_4	**3c** (43)[c]
4	**2d**	*p*-Cl–C_6H_4	**3d** (62)
5	**2e**	*o*-Cl–C_6H_4	**3e** (87)
6	**2f**	*p*-CN–C_6H_4	**3f** (88)
7	**2g**	4-Pyridyl	**3g** (73)
8	**2h**	3-Pyridyl	**3h** (68)
9	**2i**	2-Pyridyl	**3i** (82)

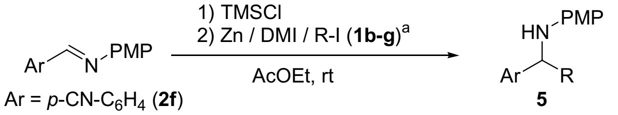
[a] Reagents and conditions: *n*-heptyl iodides (**1a**) (4.5 mmol), zinc metal (4.6 mmol), DMI (6.0 mmol), TMSCl (0.14 mmol) and AcOEt (4.5 mL) at 60 °C for 2 h.

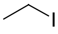
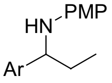
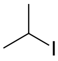
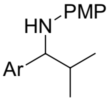
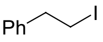
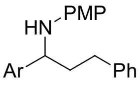
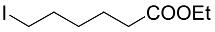
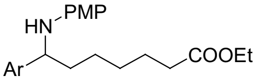
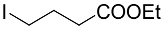
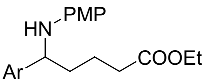
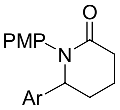
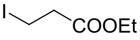
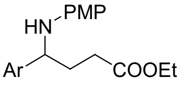
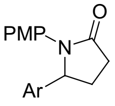
[b] Isolated yield.

[c] After silica gel chromatography purification, imines **2b**,**c** were recovered as the corresponding aldehydes in the yields of 17% and 44%, respectively.

Further applications of the reaction were studied by using various types of alkyl iodides and iodo esters (Table 3). The reaction of **2f** with nonactivated primary and secondary alkyl iodides gave the corresponding α-alkylbenzylamines in good to excellent yields (entries 1–3). Iodo esters such as ethyl 6-iodohexanoate (**1e**), ethyl 4-iodobutyrate (**1f**), ethyl 3-iodopropionate (**1g**), also smoothly reacted with **2f** in the presence of zinc powder to provide the corresponding amino acids in good yields; especially in the case of **1f** and **1g**, lactams **6**

Table 3. The zinc-promoted reactions of alkyl iodides **1** with aldimine **2f**



Entry	R–I	Time (h)	Product (yield, %)^b
1	 **1b**	2	 **5a** (82)
2	 **1c**	2	 **5b** (91)
3	 **1d**	18	 **5c** (78)
4	 **1e**	18	 **5d** (65)
5	 **1f**	18	 **5e** (10) +  **6** (78)
6	 **1g**	18	 **5f** (15) +  **7** (45)

[a] Reagents and conditions: alkyl iodides (4.5 mmol), zinc metal (4.6 mmol), DMI (6.0 mmol), TMSCl (0.14 mmol) and AcOEt (4.5 mL) at 60 °C for 2 h.
[b] Isolated yield.

and **7** were predominantly obtained in the yields of 78% and 45%, respectively.

Although the mechanistic details still remain ambiguous, the reaction may proceed through in situ generated zinc reagents as the reaction intermediate. These organozinc compounds gave the product amines through a subsequent nucleophilic addition of aldimines. In this reaction, the role of the additives (DMI or NMP) may be postulated mainly in two ways, that is, one is enhancement of nucleophilicity and the other is reduction of the basicity of organozinc compounds by coordination of additives to zinc reagents. TMSCl may activate the zinc metal surface[1c,8] and the C=N bond of aldimines by coordination.[16]

In summary, we have demonstrated that the in situ generated zinc reagents from the reaction of zinc powder with nonactivated iodides in the presence of TMSCl and DMI smoothly reacted with aromatic aldimines to give the corresponding α-alkylbenzylamine derivatives in good to excellent yields. Adaptation of this system to aliphatic aldimines and application to an asymmetric version are now under investigation.

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15. Representative procedure is as follow: Under argon atmosphere, to a mixture of zinc metal (303 mg, 4.6 mmol) and DMI (0.65 mL, 6.0 mmol) in AcOEt (4.5 mL) was added TMSCl (0.02 mL, 0.14 mmol) at 60 °C and stirred for 5 min, followed by addition of *n*-heptyl iodide (**1a**) (0.74 mL, 4.5 mmol) and stirring at the same temperature for 2 h and cooling to room temperature. Under argon atmosphere, to a suspension of imine **2f** (709 mg, 3.0 mmol) in AcOEt (2.0 mL) was added TMSCl (0.57 mL, 4.5 mmol) at room temperature and stirred for 10 min, followed by addition of organozinc reagent and stirring at same temperature. After stirring for 18 h, 1 M HCl was added to the reaction mixture and extracted with AcOEt (2×20 mL). The combined AcOEt extract was washed with 10% $NaHSO_3$ aq and brine and dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel (6:1, hexane/AcOEt) to give the product **3f** (883 mg, 88%) as yellow oil. All new compounds were fully characterized by ^{1}H, ^{13}C NMR and MS spectrometry. Selected spectra data: **3f**, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (2H, d, $J = 8.3$ Hz), 7.44 (2H, d, $J = 8.3$ Hz), 6.67 (2H, d, $J = 9.0$ Hz), 6.39 (2H, d, $J = 9.0$ Hz), 4.25 (1H, t, $J = 6.6$ Hz), 3.84 (1H, br s), 3.68 (3H, s), 1.76–1.67 (2H, m), 1.40–1.19 (10H, m), 0.86 (3H, t, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 150.5, 141.0, 132.4, 127.2, 118.9, 114.8, 114.4, 110.6, 58.88, 55.65, 38.75, 31.67, 29.35, 29.03, 26.92, 26.12, 22.53, 13.98; EI-MS *m*/*z* (relative intensity) 336 [M^+, 33], 237 (100), 122 (4.9); EI-HRMS calcd for $C_{22}H_{29}N_2O$ [M^+] 336.2202, found 336.2209.
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