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NUCLEOPHILIC AROMATIC SUBSTITUTION ON AROMATIC ALDIMINES[Ψ]

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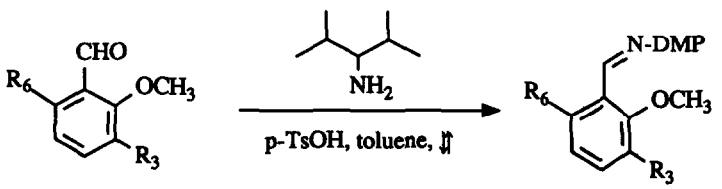
Abstract: Ortho-methoxy-substituted benzaldimines derived from 3-amino-2,4-dimethylpentane undergo efficient nucleophilic aromatic substitution with typical organolithium reagents. The aldimine products can be hydrolyzed under mild conditions to provide ortho-alkyl or ortho-phenyl benzaldehyde derivatives.

Prior to a 1975 report that 2-(2-methoxyphenyl)-4,4-dimethyl-2-oxazoline and 2-(2,3-dimethoxyphenyl)-4,4-dimethyl-2-oxazoline react with organolithium and Grignard reagents to give nucleophilic aromatic substitution of the ortho-methoxy group, S_NAr reactions with organometallic reagents were rare and limited in scope.[1] Over the years since its discovery, the oxazoline-activated S_NAr reaction has burgeoned dramatically in scope and synthetic importance.[2] Driven in part by the large number of complex aromatic structures that can be built up by S_NAr reactions, considerable effort has been directed toward synthetic transformation of the oxazoline group into a wide range of useful functionality.[2] Several practical solutions to the oxazoline→aldehyde transformation have appeared;[3] however, all of the known methods require two or more synthetic steps and employ some combination of alkylating agents, reducing agents, or oxidants. We now report the first successful examples of nucleophilic aromatic substitution on benzaldimines[4] using common organolithium reagents (n-BuLi, t-BuLi, PhLi, and 2-propenyllithium); hydrolysis of the product aldimines afforded corresponding benzaldehyde derivatives in generally good yield.

The benzaldimines used in this study were readily prepared from the appropriate aldehydes with 3-amino-2,4-dimethylpentane (1.1 equiv amine, toluene, cat. p-TsOH). Aldimines **1-3** reacted



(DMP = 2,4-dimethylpent-3-yl)

1; $R_3=R_6=H$
2; $R_3=CH_3O$, $R_6=H$
3; $R_3=H$, $R_6=CH_3O$

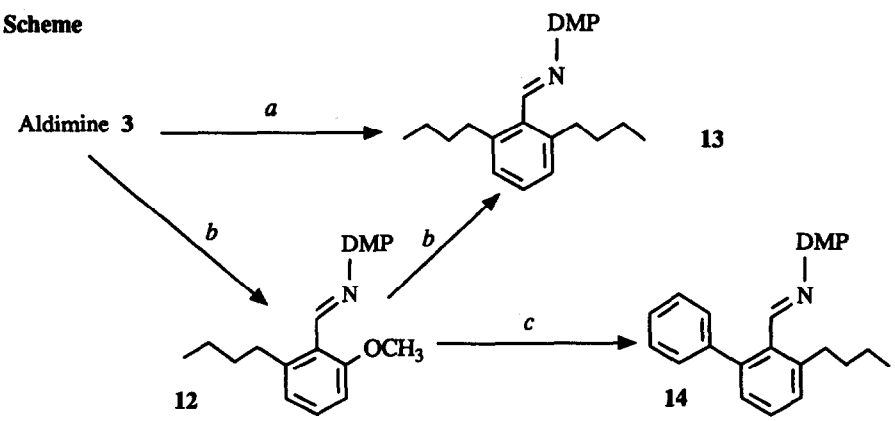
smoothly with 1.1-1.5 equiv of n-BuLi (THF-hexane, -10 to -15 °C, 1-1.5 h) to provide aldimine

products **4**, **7** and **12**, respectively. Hydrolysis of these products (5 equiv of aqueous 4 M HCl in THF solution, reflux, 45 min-1.5 h) gave corresponding aldehydes **15**, **17** and **20** (Table). Phenyllithium in THF solution also reacted cleanly, though more slowly than n-BuLi, with aldimines **1**, **2**, and **12** (2.2 equiv PhLi, -10→20 °C, 12-16 h).[5] 2-Lithiopropene reacted sluggishly with aldimine **2**; however, 6-8 equiv of this organometallic reagent (THF, -10 °C→20 °C, 1 h) gave complete conversion to aldimine **10**. The relatively low reactivities of phenyllithium and 2-propenyllithium were overcome by using these reagents in diethyl ether solution; thus, PhLi reacted with imines **1** and **2** (1.2 equiv PhLi, ether, -78→20 °C, 0.5-2.5 h) to give imines **5** and **8**, respectively, in excellent yield (entries 3 and 7, Table). Similarly, 1.2 equiv of 2-propenyllithium reacted with **2** (ether, -78→20 °C, 0.5 h) to give imine **10** in 96 % yield (entry 10, Table). *Organolithium addition to the C=N bond of the starting materials was not observed under any of the reaction conditions outlined above.*

On the other hand, methyllithium reacted with **2** (1.2 equiv CH_3Li, THF, 0 °C, 1h) to give a mixture of aldimine **11**, C=N addition product **11a** and starting material in a 1:2:2 ratio (entry 11, Table). Surprisingly, methyllithium in THF solution did not appreciably react with **2** over 1 h at -30 °C. Methylmagnesium bromide was also unreactive with **2** (1.2 equiv CH_3MgBr, THF, 20 °C, 20 h; then reflux, 6 h); indeed, aldimine **2** was recovered from this reaction mixture in good yield and pristine condition. Aldimine **1** reacted with t-BuLi (1.1 equiv t-BuLi, THF, -45 °C, 45 min) to give a 2:4:1 mixture of **6**, **6a** and starting material, respectively (entry 4, Table); under identical conditions aldimine **2** gave a 6:1 mixture of **9** and **9a**. Compound **9** was isolated and hydrolyzed (CH_3I, 2 days, 20 °C; then NaOH-H_2O-THF) to give aldehyde **19** in 38 % overall yield from **2** (entry 8, Table).

We next turned our attention to strategies for the difunctionalization of aldimine **3** (Scheme).

Scheme

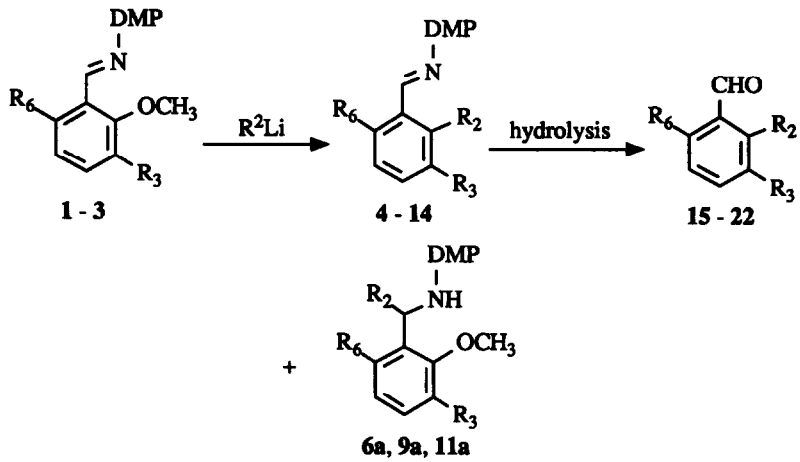


a. 2.6 equiv n-BuLi-THF; -10 °C; 2h. *b*. 1.1-1.3 equiv n-BuLi-THF; -10 °C; 1.5h. *c*. 2.2 equiv PhLi-THF; room temperature; 1.5h.

Compound **3** reacted with 1.1 equiv of n-BuLi (THF, -10 °C, 1.5 h) to give aldimine **12** (entry 12, Table). Aldimine **12** reacted smoothly with 1.3 equiv of n-BuLi to give 2,6-di-n-butyl derivative

13 (entry 13, Table). Alternatively, **3** reacted directly with 2.6 equiv of n-BuLi to give **13** in high yield (entry 14, Table). Aldimine **12** reacted with 2.2 equiv of PhLi (THF, 20 °C, 15 h) to give compound **14**.[6] Acid hydrolysis of imines **12-14** (5 equiv of aqueous 4 M HCl in THF, reflux, 2-4 h) readily afforded the corresponding aldehydes (entries 12, 13 and 15, Table).

Table: S_NAr reactions of 2,4-dimethylpent-3-yl (DMP) imines.



entry	starting imine	product imine; R_2 (%)[a]	aldehyde (%)[c]
1	**1**; R_3=R_6=H	**4**; R_2=n-Bu (98%)	**15** (70%)
2	**1**	**5**; R_2=Ph (85%)	**16** (60%)
3	**1**	**5** (93%)	**16** (95%)[d]
4	**1**	**6**:**6a**:**1**=2:4:1; R_2=t-Bu	---
5	**2**; R_3=CH_3O;R_6=H	**7**; R_2=n-Bu (95%)	**17** (94%)[d]
6	**2**	**8**; R_2=Ph (100%)	**18** (94%)[d]
7	**2**	**8** (100%)[e]	**18** (84%)
8	**2**	**9**:**9a**=6:1; R_2=t-Bu	**19** (38%)
9	**2**	**10**; R_2=2-propenyl (60%)[b]	---
10	**2**	**10** (96%)[e]	---
11	**2**	**11**:**11a**:**2**=1:2:2; R_2=CH_3	---
12	**3**; R_3=H;R_6=CH_3O	**12**; R_2=n-Bu (100%)	**20** (73%)
13	**12**; R_3=H;R_6=n-Bu	**13**; R_2=R_6=n-Bu (85%)	**21** (72%)
14	**3**	**13** (98%)	---
15	**12**	**14**; R_2=Ph (100%)	**22** (59%)

[a]Crude yield. The crude imines were estimated to be ≥95 % pure by ^{1}H NMR (300 MHz). [b]Imine isolated by alumina chromatography (99:1 hex-EtOAc). [c]Aldehydes were isolated by silica gel chromatography (hex-EtOAc) or by vacuum distillation with a kugelrohr apparatus unless otherwise noted. [d]Crude yield. Aldehyde estimated at ≥95 % purity by ^{1}H NMR (300 MHz).[e]Reaction carried out in diethyl ether.

Further investigations are currently underway in our laboratory to more fully define the scope and potential synthetic utility of S_NAr reactions of organometallic reagents on aromatic aldimines.[7]

References and Notes

Ψ Contribution #862 from the Institute of Organic Chemistry. This paper is dedicated to Dr. John A. Edwards on the occasion of his retirement.

1. Meyers, A. I.; Mihelich, E. D. *J. Am. Chem. Soc.*, **1975**, *97*, 7383 and references therein.
2. For a review see Reuman, M.; Meyers, A. I. *Tetrahedron*, **1985**, *41*, 837.
3. (a) Nordin, I. C. *J. Heterocyclic. Chem.*, **1966**, *3*, 531. (b) Wilson, S. R.; Mao, D. T.; Khatri, H. N. *Synthetic. Commun.*, **1980**, *10*, 17. (c) Meyers, A. I.; Himmelsbach, R. J.; Reuman, M. *J. Org. Chem.*, **1983**, *48*, 4053. (d) Barner, B. A.; Meyers, A. I. *J. Am. Chem. Soc.*, **1984**, *106*, 1865.
4. During the course of preparation of this manuscript a method for S_NAr reaction of naphthaldimines with 1-lithionaphthalene was reported: Shindo, M.; Koga, K.; Tomioka, K. *J. Am. Chem. Soc.*, **1992**, *114*, 8732.
5. When an equivalent each of aldimine **1** and 2-(2-methoxyphenyl)-4,4-dimethyl-2-oxazoline[1] were allowed to compete for 0.8 equiv of PhLi (THF, 0 °C, 3 h) the crude product consisted of a 1:0.7:0.3 mixture of unchanged aldimine **1**, 2-(biphenyl)-4,4-dimethyl-2-oxazoline, and unchanged 2-(2-methoxyphenyl)-4,4-dimethyl-2-oxazoline, respectively (^{1}H NMR analysis). Thus, the 2,4-dimethylpent-3-ylimine group is clearly a weaker S_NAr activating group than the oxazoline functionality. A quantitative assessment of the relative activating strength of the two groups awaits further study.
6. It is not yet clear whether there are significant mechanistic differences between the S_NAr reactions of aromatic oxazolines and aldimines. Meyers has reported that 2.5 equiv of PhMgBr reacts with 2-(2,6-dimethoxyphenyl)-4,4-dimethyl-2-oxazoline to give a 1:1 mixture of mono- and diphenyl adducts. Surprisingly, the isolated mono-phenyl adduct is reported to be resistant toward further reaction with PhMgBr: see Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.*, **1978**, *43*, 1372.
7. For example, in an unoptimized procedure 1.5 eq of 2-lithioanisole reacted with imine **2** (ether-hexane; -78 °C→RT; 3 h) to give, after acid hydrolysis of the product imine, isolated 2,2'-dimethoxy-6-formylbiphenyl in 57 % yield. 2,2'-Dimethoxy-6-formylbiphenyl has been prepared by an alternate 7-step procedure in 40 % overall yield: see *Organic Syntheses*, **1992**, *Vol. 71*, 107.
8. ^{1}H and ^{13}C NMR spectra of imines **1-14** and benzaldehyde derivatives **15-22** were in complete accord with the proposed structures. Satisfactory combustion analyses were obtained for compound **19** and the 2,4-DNP derivatives of compounds **15-18** and **20**.

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