Tetrahedron Letters,Vol.24,No.49,pp 5465-5468,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

ORTHO METALATION DIRECTED BY α-AMINO ALKOXIDES. AN IMPROVED SYNTHESIS OF ORTHO-SUBSTITUTED ARYL KETONES

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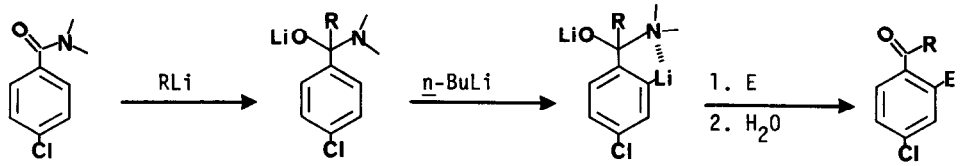
Summary: Ortho-substituted aryl ketones are prepared from N-[2-(dimethylamino)ethy]-N-methylbenzamides via ortho lithiation of intermediate α-amino alkoxides, formed in situ by addition of RLi. An ortho lithiation of N-[2-(dimethylamino)ethyl]-N-methylbenzamide is also described.

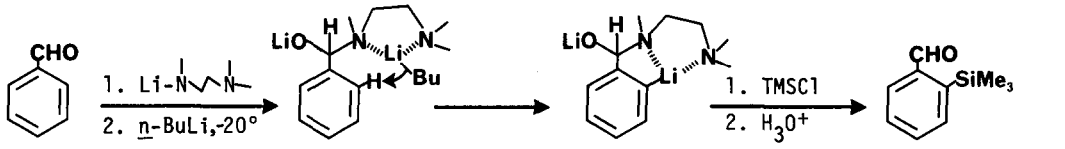
Tertiary α-amino alkoxides, formed in situ by the addition of an organolithium reagent to a tertiary arylcarboxamide, can be ortho-lithiated and alkylated to provide ortho-subsituted aryl ketones.[1-3] This method works well for the directed α-metalation of thiophenes[1] and furans[2] due to their ease of deprotonation. Gschwend and co-workers[3] have reported using this method with benzenoid systems. They converted N,N-dimethyl-p-chlorobenzamide (1) directly into ortho-substituted aryl ketones 2 via addition of RLi followed by ortho lithiation and reaction with an electrophile. However, the α-(N,N-dimethylamino) alkoxide group is not a strong ortho director, and the isolated yields of 2 are only moderate.[3] To make this method general and useful for a variety of benzenoid systems, a more powerful ortho directing α-amino alkoxide group is needed.



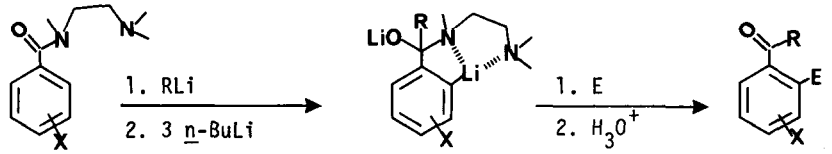
1 2

Recently in our laboratories we have been studying the chemistry of α-amino alkoxides.[4-6] We have reported a novel one-pot ortho alkylation of aromatic aldehydes via ortho-lithiated α-(N-methylpiperazino)benzyl alkoxides.[5] The intermediate α-amino alkoxides were formed in situ via the addition of aryl aldehydes to lithium N-methylpiperazide in benzene. The α-(N-methylpiperazino) alkoxide group proved to be a weak ortho director and vigorous metalation conditions (3 n-BuLi, benzene, reflux) were needed to effect ortho lithiation.[5] It was subsequently discovered that the metalation rate could be dramatically increased by varying the amine component of the α-amino alkoxide.[6] For example, when N,N,N'-trimethylethylenediamine was used as the amine

component, benzaldehyde could be ortho-metalated-silylated at low temperature in high yield as shown below. The metalation rate increase is undoubtedly due to an intramolecular TMEDA-like assisted metalation.[6]



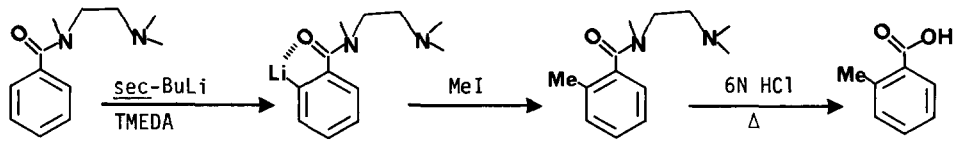
We have applied the diamine concept to the Gronowitz-Gschwend procedure for the synthesis of ortho-substituted aryl ketones as shown below. The results are given in the table. The yields are high and the method is clearly superior to the original version



3 4

using N, N-dimethylbenzamides. This is most evident in the synthesis of 3-chloro-2-(methylthio)acetophenone (entry 8), where ortho lithiation-alkylation must occur at low temperature to prevent benzyne formation.[7] Under the same conditions, N,N-dimethyl-3-chlorobenzamide gave mainly 3-chloroacetophenone (80%) and only a trace (<1%) of the desired ortho-substituted product (entry 9).

The N-[2-(dimethylamino)ethyl]-N-methylbenzamides undergo nucleophilic attack by lithium reagents as demonstrated, however, with sec-BuLi/TMEDA at -78°C (THF) addition does not occur and ortho lithiation results. This of course is directly analogous to the ortho lithiation of N,N-diethylbenzamides, a powerful methodology initially introduced by Beak and Brown.[8] The main disadvantage of the N,N-diethyl amide as an ortho metalation directing group is its resistance to hydrolysis.[9] In contrast, the amino amide 5 is easily hydrolyzed with 6N HCl(reflux) to o-toluic acid (6).[10] This new ortho-directing group should compliment Beak's methodology, and work is in progress toward that goal.



(inverse addition)[15] 5 55% 6 81%

Aknowledgements. Financial support of this work by the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

Table Synthesis of Ortho-Substituted Aryl Ketones From Tertiary Benzamides

Entry	Amide	Reaction Conditions[a]	E	Product[b]	Yield[c] %	mp, °C (lit. mp)
1	N,N-dimethyl benzamide	1) 1.5 MeLi, PhH, 0°, 1/2 h 2) 3 n-BuLi, RT, 5h	MeI	o-methyl-acetophenone	33[d]	---
2	3, X = H	1) 1.5 MeLi, PhH, 0°, 1/2 h 2) 3 n-BuLi, RT, 5h	MeI	o-methyl-acetophenone	77 (88)[d]	2,4-DNP 160-162 (161-162)[11]
3	3, X = H	1) 1.1 n-BuLi, PhH, 0°, 1/2 h 2) 3 n-BuLi, RT, 24h	MeI	o-methyl-valerophenone	55	2,4-DNP 75-77 (76-78)[11]
4	3, X = H	1) 1.1 n-BuLi, PhH, 0°, 1/2 h 2) 3 n-BuLi, RT, 24h	MeSSMe	o-(methylthio)-valerophenone	77	2,4-DNP 130-132, b
5	3, X = H	1) 1.5 PhLi, PhH, 0°, 1/2 h 2) 3 n-BuLi, RT, 12h	MeI	o-methyl-benzophenone	85	oxime 114-116 (116)[12]
6	3, X = p-Cl	1) 1.5 MeLi, THF, -20°, 3/4 h 2) 3 n-BuLi, -20°, 4h	MeSSMe	o-(methylthio)-chloroacetophenone	85	62-63 (62)[3]
7	3, X = p-Cl	1) 1.5 MeLI, THF, -20°, 3/4 h 2) 3 n-BuLi, -20°, 4h	MeI	o-methyl-p-chloroacetophenone	87	oxime 68-69 (69)[13]
8	3, X = m-Cl	1) 1.5 MeLi, THF, -78°, 3/4 h 2) 3 n-BuLi, -78°, 7h	MeSSMe	o-(methylthio)-m-chloroacetophenone	63	2,4-DNP 107-108, b
9	N,N-dimethyl-m-chlorobenzamide	1) 1.5 MeLi, THF, -78°, 3/4 h 2) 3 n-BuLi, -78°, 7h	MeSSMe	o-(methylthio)-m-chloroacetophenone	1[d]	---
10	N,N-dimethyl-p-methoxybenzamide	1) 1.5 MeLi, PhH, RT, 4h 2) 3 n-BuLi, THF, -20°, 24h,	MeI	o-methyl-p-methoxyacetophenone	2[d]	---
11	3, X = p-OMe	1) 1.5 MeLi, PhH, RT, 4h 2) 3 n-BuLi, THF, -20°, 24h	MeI	o-methyl-p-methoxyacetophenone	83	semicarbazone 198-200 (198-200)[14]

[a]Reactions were performed on a 3-mmol scale. THF was added to the reaction mixtures in benzene prior to cooling to -42°C and adding the electrophile (6 equiv). The workup consisted of pouring the reaction mixture into stirred cold 10% aqueous HCl followed by extraction with ether.

[b]All products gave the expected IR and ^{1}H NMR spectra. New products, from entries 4 and 8, gave satisfactory analytical data.

[c]Yields are for isolated, pure, material obtained from preparative layer chromatography (silica gel, acetone-hexanes).

[d]GC yield.

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(Received in USA 9 September 1983)