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META FUNCTIONALIZATION OF ANILINES AND PHENOL

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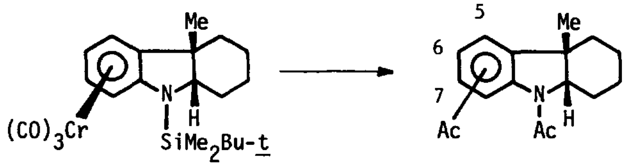
Regioselective introduction of various functional groups on the meta-position of anilines and phenol was achieved by proton abstraction from the chromium tricarbonyl complexes **3**,**5**,**7** with *n*-BuLi, followed by the addition of electrophiles and decomplexation.

Base promoted proton abstraction from simple aromatic rings is known to be facilitated by chromium tricarbonyl complex formation.[1] Therefore, even in anilines and phenols, when their aromatic rings are activated by the formation of chromium tricarbonyl complex and the heteroatom-promoted ortho metalation[2] is effectively prevented by a bulky blocking group on the heteroatoms, meta or para positions are expected to be metalated by a alkyl lithium treatment. In fact, in an effort to introduce functionalized substituents on the aromatic rings of indoline alkaloids, π-(9-*t*-butyldimethylsilyl-4a-methyl-1,2,3,4,4a,9a-hexahydrocarbazole)chromium tricarbonyl (**1**), for example, was found to afford, after a series of operations (*n*-BuLi treatment, addition of acetaldehyde, oxidative decomplexation, and Jones oxidation of the resulting alcohol), 5-, 6-, and 7-acetyl derivatives **2a**,**b**,**c** in a ratio of 2:1:7 (total yield, 59%).[3] This unexpectively high meta/para ratio (9/1) prompted us to investigate this reaction in detail in a more simplified system.



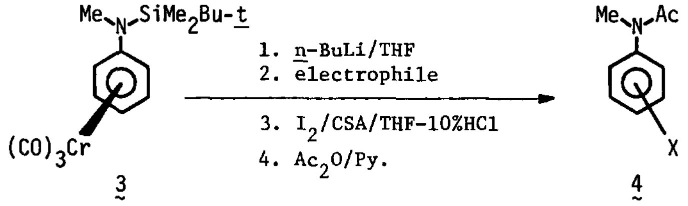
1

2a: 5-Ac
b: 6-Ac
c: 7-Ac

Initially, π-(*N*-*t*-butyldimethylsilyl-*N*-methylaniline)chromium tricarbonyl (**3**),[4] prepared in 98% yield from π-(aniline)chromium tricarbonyl by *N*-silylation (*n*-BuLi/*t*-$BuMe_2SiCl$/THF) followed by *N*-methylation (*n*-BuLi/MeI/THF), was chosen as a substrate. Metalation of **3** was carried out i) *n*-BuLi(2 equiv)-TMEDA(tetramethylethylenediamine, 3 equiv) in THF at -60°C for 3 h —— method A or ii) *n*-BuLi(4 equiv) in THF at -40°C for 30 min —— method B[1b] and the resulting species was quenched by the electrophiles. Oxidative removal of the chromium tricarbonyl moiety by iodine in 10%-HCl[5]/THF in the presence of camphorsulfonic acid (CSA), followed by Ac_2O/Py. treatment, afforded the *N*-methylacetanilide derivatives **4**. The results were shown in Table 1.

As was expected, no ortho-substituted products were obtained in each case. The particular feature of the present reaction is that a remarkably high meta to para substitution ratio was

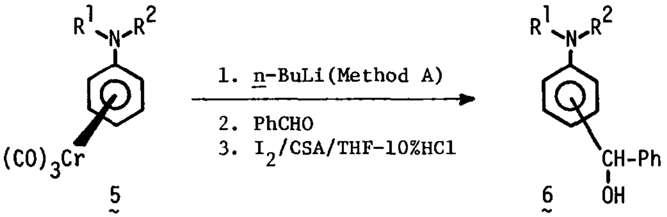
Table 1. Lithiation of π-(*N*-*t*-Butyldimethylsilyl-*N*-methylaniline)chromium Tricarbonyl (**3**) and Reactions with Electrophiles.



entry	electrophile	method of metalation[a]	product **4** (X)	yield(%)	ratio of isomers[c] ortho:meta:para
1	PhCHO	A	CH(OH)Ph[b]	69	0 : 98 : 2
2	PhCHO	B	CH(OH)Ph[b]	62	0 : 95 : 5
3	MeCHO	A	CH(OH)Me	57	0 : 96 : 4
4	$HCONMe_2$	A	CHO	61	0 : 98 : 2
5	MeI	B	Me	73	0 : 86 : 14
6	MeSSMe	A	SMe	73	0 : 85 : 15
7	PhCN	A	COPh	73	0 : 86 : 14

a. Method A: *n*-BuLi(2 equiv)-TMEDA(3 equiv)/-60°C/3 h; Method B: *n*-BuLi(4 equiv)/-40°C/30 min.
b. In these cases, *O*,*N*-diacetylation takes place by acetylation with Ac_2O/Py. Subsequent KOH/MeOH treatment causes de-*O*-acetylation selectively affording **4** [X=CH(OH)Ph or CH(OH)Me].
c. The isomer ratios were determined by gas chromatography. The structures of the products were unequivocally confirmed by comparing the IR, NMR, and GC-MS spectra with those of the authentic samples.

Table 2. Reaction of Lithio π-(Anilines)chromium Tricarbonyl with Benzaldehyde.



a: R^1=Me, R^2=CH_2Bu-*t*
b: R^1=Et, R^2=CH_2Bu-*t*
c: R^1=Me, R^2=Ph
d: R^1=Et, R^2=Ph

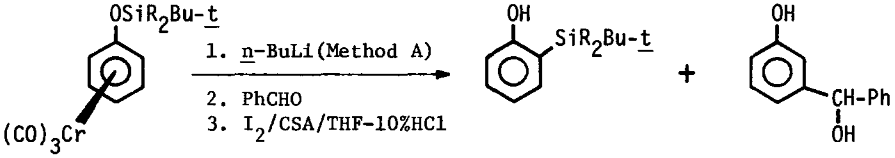
entry	substrate	product	yield(%)	ratio of isomers[a] ortho:meta:para
1	**5a**	**6a**	74	14 : 76 : 10
2	**5b**	**6b**	64	1 : 99 : 0
3	**5c**	**6c**	64	29 : 71 : 0
4	**5d**	**6d**	68	17 : 83 : 0

a. See Table 1, footnote c.

obtained in entry 1 ~ 4, where electrophiles were carbonyl compounds. Even in entry 5 ~ 7, a predominance of the meta-substitution (*m*:*p*=85:15) is evident, compared to the results obtained by metalation and subsequent alkyl halide treatment of π-(ethylbenzene)- or π-(*t*-butylbenzene)-chromium tricarbonyl, where substitution ratio on meta- and para-positions are roughly estimated to be 2:1 or 3:2, respectively.[1b,6]

When *t*-butyldimethylsilyl protecting group was replaced by *neo*-pentyl group, selectivity was much reduced and appreciable amounts of both ortho and para isomers were obtained (Table 2, entry 1). However, when *N*-methyl group was also replaced by *N*-ethyl group, the meta isomer was obtained almost as a sole product (Table 2, entry 2). *N*-Phenyl derivatives **5c** and **5d** gave appreciable amounts of the ortho isomers, but again none of the para isomers were obtained (Table 2, entry 3,4).

Then, π-(*t*-butyldimethylsilyloxybenzene)chromium tricarbonyl (**7a**) was subjected to the metalation with *n*-BuLi-TMEDA and the resulting species was quenched with benzaldehyde. Subsequent decomplexation with iodine/CSA afforded 2-*t*-butyldimethylsilyl phenol (**8a**) and 3-(α-hydroxybenzyl)phenol (**9**) in 35 and 40% yields, respectively. When the phenol oxygen was blocked with a still bulky *t*-butyldiphenylsilyl group, formation of **8b** was suppressed to 19% but that of **9** was improved to 48%. Here again, none of the para isomer was obtained. The formation of **8a**,**b** clearly indicates that ortho-lithiation took place in this case.

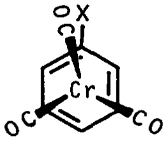


7a: R=Me
b: R=Ph

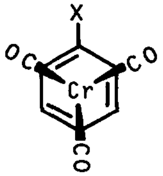
8a: R=Me
b: R=Ph

9

Trahanovsky[1b] has suggested a possibility that proton abstraction is preceded by formation of an adduct involving coordination of butyllithium to an oxygen of a carbonyl ligand and then a butyl anion abstracts a hydrogen from the aromatic carbon eclipsed to the carbonyl ligand.[7] Since π-(*N*-*t*-butyldimethylsilyl-*N*-methylaniline)chromium tricarbonyl (**3**) has been determined to have an eclipsed structure **i**[8] [X=N(Me)SiMe$_2$Bu-*t*] by X-ray crystallography,[9] its high meta substitution ratio would be rationallized, at least in part,[10] by taking account of the above assumption.



i



ii

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References and Notes

(1) (a) M. F. Semmelhack, J. Bisaha, and M. Czarny, J. Am. Chem. Soc., 101, 768 (1979).
  (b) R. J. Card and W. S. Trahanovsky, J. Org. Chem., 45, 2560 (1980), and references cited therein.
  (c) M. Uemura, N. Nishikawa, and Y. Hayashi, Tetrahedron Lett., 2069 (1980).

(2) H. W. Gschwend and H. R. Rodriguez, "Org. Reaction", Vol. 26, Ed. by W. G. Dauben, John Wiley & Sons Inc., New York, 1979, pp 1.

(3) M. Fukui, Y. Yamada, A. Asakura, and T. Oishi, Heterocycles, 15, 415 (1981).

(4) Satisfactory elemental analytical data were obtained for all new crystalline compounds.

(5) Oxidative removal of chromium tricarbonyl moiety from π-(anilines)chromium tricarbonyl by iodine should be carried out in acidic media because, in neutral media, the resulting anilines were presumed to be converted to p-iodoanilines; T. Oishi, M. Fukui, and Y. Endo, Heterocycles, 7, 947 (1977); M. Fukui, Y. Endo, and T. Oishi, Chem. Pharm. Bull. (Tokyo), 28, 3639 (1980).

(6) The meta/para substitution ratios of base-induced alkylation of ethylbenzene, cumene, and t-butylbenzene are known to be statistical (2:1); C. D. Broaddus, J. Org. Chem., 35, 10 (1970).

(7) cf. G. R. Dobson and J. R. Raxson, J. Am. Chem. Soc., 95, 5925 (1973).

(8) The tricarbonyl groups in 3 would be rotating rapidly in solution. However, it has been claimed that when X is electron-donating groups, an eclipsed conformer i is favoured over other conformers including an eclipsed conformer ii both in solution [A. Solladié-Cavallo and J. Suffert, Org. Magn. Reson., 14, 426 (1980); A. Solladié-Cavallo and G. Wipff, Tetrahedron Lett., 3047 (1980)] and in solid phase [O. L. Carter, A. T. McPhail, and G. A. Sim, J. Chem. Soc. (A), 822 (1966); Idem., ibid., 228 (1967)].

(9) Crystal data, final atomic parameters, and anisotropic temperature factors have been deposited with the Cambridge Crystallographic Data Centre. The X-ray analysis was carried out by Dr. Toshio Sakurai and Miss Kimiko Kobayashi of this Institute. We are indebted to them for their expert assistance.

(10) The bulkyness of substituents of the nitrogen atom should also affect the meta/para ratio, since π-(N,N-dimethylaniline)chromium tricarbonyl gives much unsatisfactory result (3:1).[1b] The reason for this and why carbonyl electrophiles give a much better meta/para substitution ratio compared to other electrophiles remains unsolved.

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