

FUNCTIONALIZATION OF C-6 POSITION OF INDOLINES

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Lithiation of π -(N-t-butyldimethylsilylindolines)chromium tricarbonyl by n-BuLi in the presence of TMEDA followed by the addition of aldehydes produced 4-, 5-, and 6-substituted indolines, the last ones being major products. 5- and 6-methoxyindolines were obtained from the corresponding addition products.

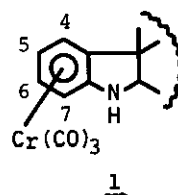
In an effort to introduce oxygen functions into aromatic rings of indolines, nucleophilic substitution reactions of 5-chloroindolines with a methoxide anion were found to proceed smoothly providing 5-methoxyindolines when the chlorine atom was activated by π -(arene)chromium tricarbonyl (CTC-arene) complex formation and the reactivity of the methoxide anion was enhanced by the addition of 18-crown-6¹. However, we have encountered with the problem that CTC-complex formation became difficult as the complexity of chloroindolines was increased. On the other hand, indolines bearing no chlorine atom were found to give the corresponding CTC-indolines 1 in reasonable yields. Therefore, it was highly required to develop a new method to functionalize these complexes directly. To achieve this, lithiation of the activated aromatic protons by CTC-complex formation followed by the addition of electrophiles was seriously considered.

Heteroatom-promoted ortho metalations of substituted benzenes have been extensively studied².

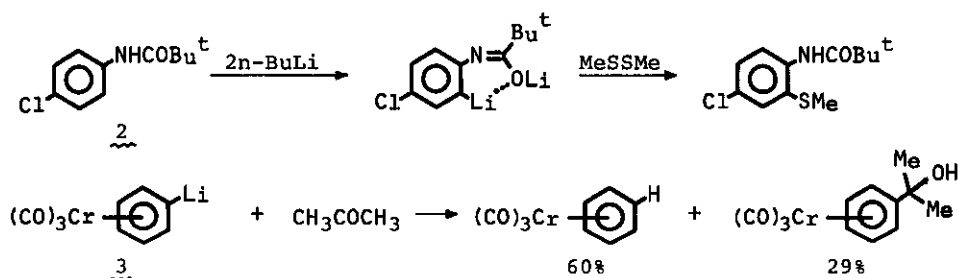
For example, N-pivaloylanilines 2 undergo ortho lithiation on n-BuLi treatment³. This means that metalation of C-4, C-5, or C-6 position of indolines

(para or meta to the nitrogen atom) can not be achieved by this technique.

However, we considered that if the C-7 position (ortho to the nitrogen atom) was



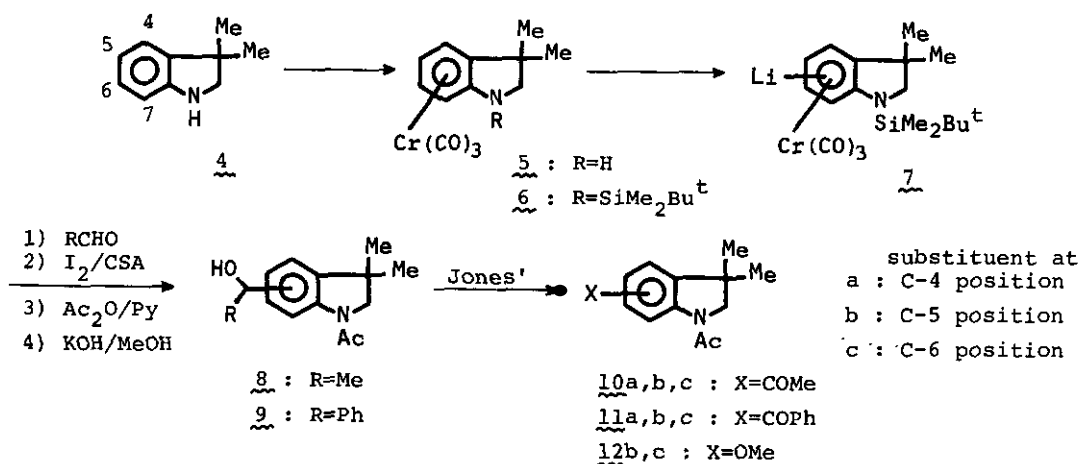
masked by bulky N-substituents and the aromatic protons were activated by CTC-complex formation⁴, proton abstraction should take place from the carbons other than C-7 position. Semmelhack et al.⁵ in their excellent work on ortho metalation of CTC-arenes and their reactions with electrophiles have reported that in the reaction of lithiated species 3 of simple CTC-benzene with acetone, proton abstraction from acetone was a major process (60%), addition of acetone being a minor process (29%).



We independently performed a series of experiments along the afore-mentioned assumption and found that lithiated species of CTC-N-t-butyltrimethylsilylindolines reacted with aldehydes producing, in contrast with Semmelhack's case, the addition products in fair yields.

CTC-3,3-Dimethylindoline 5 (mp 142-3°C) was prepared in 89% yield by treating 3,3-dimethylindoline (4) with an excess of $\text{Cr}(\text{CO})_6$ in diglyme-cyclohexane (1:1) at 125°C for 4 days. Proton abstraction from secondary amine of 5 by KH in THF in the presence of 18-crown-6 (0.25 equiv) followed by the addition of t-BuMe₂SiCl produced the N-silylated compound 6 as a stable, crystalline compound (96%, mp 140-141°C)⁶. Then, 6 was subjected to the proton abstraction using 2 equiv of n-BuLi in the presence of N,N,N',N'-tetramethylethylenediamine (TMEDA) in THF below -60°C for 3 h. The lithio derivative 7 was quenched with excess acetaldehyde and allowed to warm to room temperature. The product was then treated with excess iodine in THF-10% HCl (3:2) in the presence of camphorsulfonic acid (1.5 equiv) at room temperature to give the alcohol, which was converted to the N-acetyl derivative 8 by initial O,N-diacetylation followed by selective O-deacetylation. The compound 8 was obtained as a mixture of three positional isomers. Jones' oxidation of 8 afforded the corresponding methyl ketones 10a,b,c (53% from 6)⁷, which could be separated using the Lobar column.

In the same way, 7 was treated with benzaldehyde and the products were



converted to the benzoyl derivatives 11a,b,c (60% from 6)⁷. The results were summarized in Table I and II. Conversion of the acetyl indolines 10b and 10c into the methoxy indolines 12b (67%) and 12c (84%) were achieved by MCPBA oxidation in CHCl₃ (room temperature, 3-4 days), followed by hydrolysis of the O-acetate and methylation of the resulting phenols with MeI-K₂CO₃ in refluxing acetone. Baeyer-Villiger oxidation did not take place with 4-acetyl compound 10a, which may be ascribed to the masking by bulky 3,3-dimethyl groups.

Then, the present method was extended to the tricyclic compound 13. Two isomeric CTC-complexes were obtained in this case and the major product (79%) was assigned as 14 [mp 147-8°C, nmr(d₆-acetone): δ 1.36 (C₃-CH₃)] and the minor product (8%), as 15 [mp 152-3°C, nmr(d₆-acetone): δ 1.26 (C₃-CH₃)] from nmr data⁸. The major compound 14 was successfully converted into the acetyl derivatives 17a,b,c⁷ and replacement of acetyl groups at C-5 and C-6 positions⁹ with methoxy group proceeded smoothly to give 18b and 18c in 70 and 68% yields, respectively, in the same way as described in the dimethylindoline series (see Table I and II).

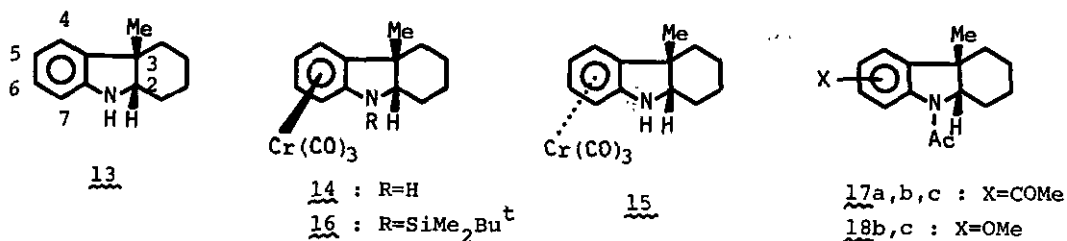


Table I. Yields of 10, 11 & 17 and Ratio of Isomers

Substrate	Electrophile	Product(X)	Yield	Ratio (a : b : c)
<u>6</u>	MeCHO	<u>10</u> (COMe)	53%	27 : 16 : 57
<u>6</u>	PhCHO	<u>11</u> (COPh)	60%	27 : 19 : 54
<u>16</u>	MeCHO	<u>17</u> (COMe)	59%	19 : 10 : 71

The particular feature of the present method is that substituents could be introduced mainly into the meta position to the nitrogen atom¹⁰, providing useful means for the preparation of otherwise difficultly accessible 6-substituted indoline derivatives. Further studies are being continued to establish the scope of these anomalous meta metalation of aromatic amines.

Table II. Physical and Spectral Data of Reaction Products^{a)}

Compd.	mp	ir cm ⁻¹ (nujol)		nmr δ (CDCl ₃)		uv nm (EtOH)
		C=O and/or NCOCH ₃	C ₇ -H	C ₃ -CH ₃		
<u>10a</u>	89-90°	1685, 1655	8.36 (br s)	1.41	238	
<u>b</u>	176-7°	1660	8.20 (br d, J=8.0Hz)	1.38	307	
<u>c</u>	107-8	1680, 1655	8.61 (s) ^{b)}	1.36 ^{b)}	244	
<u>11a</u>	191-3°	1660	8.38 (br d, J=8.0Hz)	1.36	252.5	
<u>b</u>	119-120.5°	1660, 1640	8.21 (br d, J=8.0Hz)	1.39	245, 314	
<u>c</u>	129-130°	1660	8.56 (s)	1.38	250	
<u>12b</u>	84-5°	1650	7.96 (d, J=8.4Hz) ^{b)}	1.31 ^{b)}		
<u>c</u>	87-8°	1660	7.71 (s) ^{b)}	1.28 ^{b)}		
<u>17a</u>	136-7°	1690, 1660	8.12 (br s)	1.36	239	
<u>b</u>	oil ^{c)}	1670 ^{b)}	7.98 (br s)	1.13	307	
<u>c</u>	155-6°	1675, 1645	8.60 (br s)	1.14	244	
<u>18b</u>	69-70°	1650	8.00 (br d, J=8.0Hz)	1.11		
<u>c</u>	77-80°	1655	7.76 (br s)	1.10		

a) All crystalline compounds gave satisfactory elemental analytical data.

b) Measured in CCl₄.

c) 2,4-DNP: mp 221-2°C(dec.) (recrystallized from EtOH; one molecule of EtOH is involved)

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References and Notes

1. T. Oishi, M. Fukui, and Y. Endo, Heterocycles, 1977, 7, 947.
Other relating works, see T. Hino, M. Taniguchi, A. Gonsho, and M. Nakagawa, Heterocycles, 1979, 12, 1027; K. Saito and Y. Kikugawa, J. Heterocycl. Chem., 1979, 16, 1325.
2. H. W. Gschwend and H. R. Rodriguez, "Org. Reactions", Vol 26, eds. by W. G. Dauben, J. Wiley and Sons, Inc., New York, 1979, p 1.
3. W. Fuhrer and H. W. Gschwend, J. Org. Chem., 1979, 44, 1133.
4. Without formation of CTC-complex, lithiation did not proceed at all in N-silylated indoline series.
5. M. F. Semmelhack, J. Bisaha, and M. Czarny, J. Amer. Chem. Soc., 1979, 101, 768.
6. The corresponding simple N-t-butyldimethylsilyl derivative of 4 was found to be rather unstable but could be isolated in 48% yield (bp₂ 96-7°C). The remarkable stability of 6, essential to carry out further studies, may be attributable to the decrease of nitrogen basicity owing to complex formation.
7. The structures of these isomers were determined by spectral data (see Table II). The compounds whose C-7 protons appear in the lowest field as a singlet in nmr spectra were assigned as C-6 keto derivatives (10c, 11c, 17c) since C-7 protons were located between two carbonyl groups. The compounds showing extreme red shift in uv spectra were assigned as C-5 keto compounds (10b, 11b, 17b) because the nitrogen lone pair should be well conjugated with C-5 ketone. Moreover, the structures of the C₅-OMe derivatives (12b and 18b) were confirmed by the direct comparison with the corresponding authentic samples.
8. The compound whose methyl signal appears in lower field was assigned as 14, since protons located in the same plane with Cr(CO)₃ moiety are known to shift to lower field.
9. Simple indoline numbering was tentatively adopted in these cases for better understanding.
10. Metalation of triphenylamine with n-BuLi in the presence of copper bronze has been reported to take place on the meta position but the yield was only 7%. H. Gilman and G. E. Brown, J. Amer. Chem. Soc., 1940, 62, 3208.

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