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C-2-SIDE CHAIN MODIFICATION OF 2-METHYL-3-ALKYLINDOLES VIA 3-METHYLTHIOINDOLENINES: A NEW APPROACH TO PYRROLO[1,2-a]INDOLES

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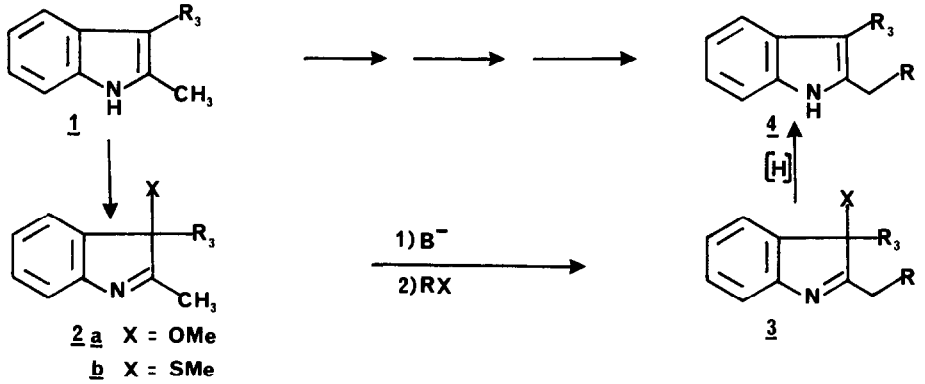
A strategy for side chain alkylation of 2-methyl-3-alkylindoles, involving deprotonation of 3-methylthioindolenines, derived from 2-methyl-3-alkylindoles by reaction with methane sulfenyl chloride, reaction with carbon electrophiles and reduction, is outlined and applied to the synthesis of pyrrolo[1,2-a] indoles.

We have recently reported a strategy for the C-2-side chain alkylation of 2-methyl-3-alkylindoles **1** involving deprotonation, alkylation and reduction of 3-methoxyindolenines **2a** (see Scheme 1) which provided a route to 2,3-dialkylindoles not readily available by more direct methods.[1] Some years ago, Gassman and co-workers reported the preparation of 3-methylthioindolenines **2b** as intermediates in a novel synthesis of indoles from anilines.[2] The possibility that side chain alkylation of 3-methylthioindolenines might not only complement our approach to synthetic elaboration of indoles via 3-methoxyindolenines **2a** but also usefully extend the scope of the Gassman synthesis of indoles, prompted us to explore the synthesis and chemistry of 3-methylthioindolenines **2b**. We have found that 2,3-dialkylindoles react readily with methanesulfenyl chloride to give the corresponding 3-methylthioindolenines **2b** in excellent yield.[3] We report herein a variety of carbon-carbon bond forming reactions involving 3-methylthioindolenines and mild selective reduction of the products to yield C-2 side chain modified indoles.

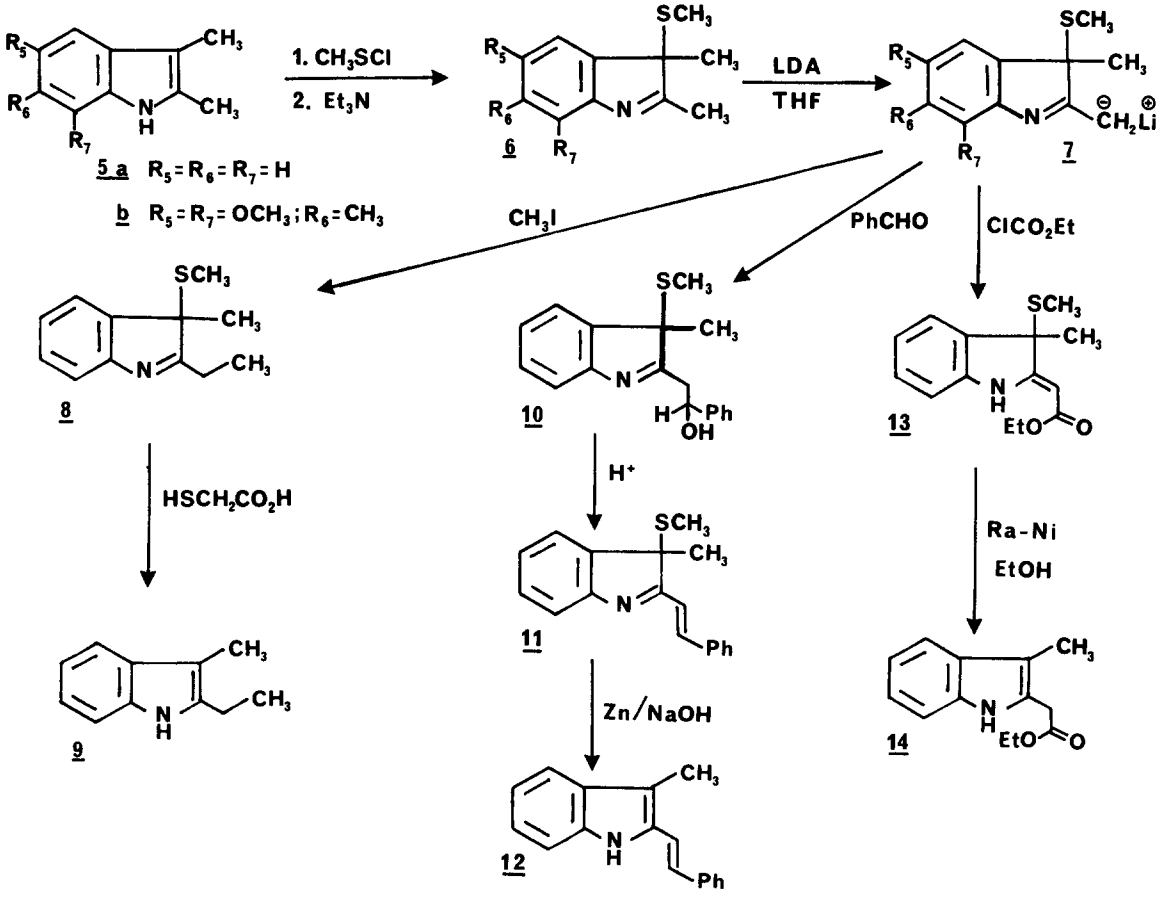
Scheme 1



The isolated indolenine **6a**, prepared from **5a** by reaction with methane sulfenylchloride as indicated in Scheme 2 was readily deprotonated at -78° by reaction with LDA in anhydrous THF and the anion **7a** was reacted with various carbon electrophiles. With methyl iodide the indolenine **8** was obtained and reduced by brief warming with mercaptoacetic acid[3] in methylene chloride to give the side chain alkylated indole **9** (65% overall yield from **5a**). Reaction of **7** with benzaldehyde gave a mixture of diastereomeric alcohols **10** which was dehydrated with acetic acid in methylene chloride to give the indolenine **11** (74%). Reduction of **11** was effected most efficiently with zinc in refluxing methanolic sodium hydroxide to yield the indole **12** (86% yield). Acylation of **7** was effected by reaction with ethyl chloroformate to give **13** (41% yield) which was resistant to reduction by mercaptoacetic acid but yielded the indole **14** in modest yield (42%) upon reaction with Raney Nickel in refluxing ethanol.

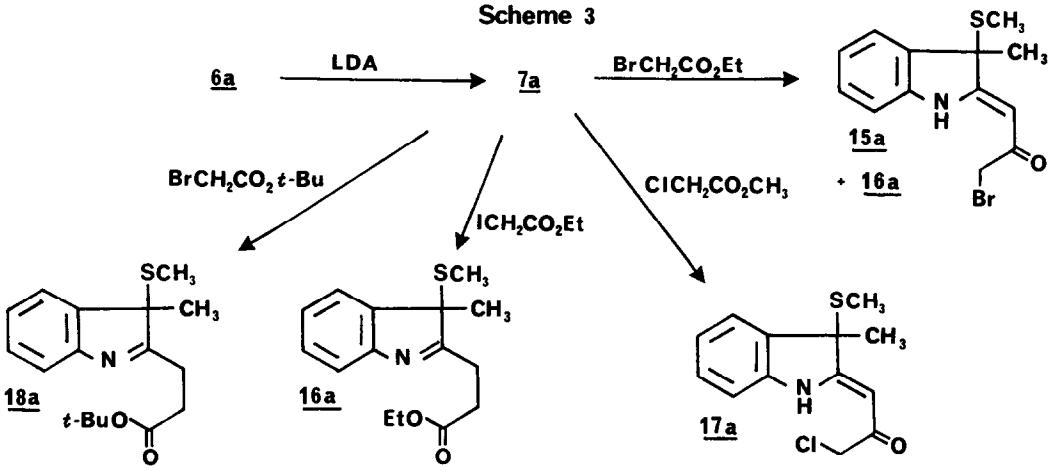
In connection with studies aimed at the total synthesis of mitomycin antibiotics we became interested in extending this methodology to the synthesis of the pyrrolo[1,2-a]indole system **20**,[6] by reaction of **7** with an appropriately substituted two carbon unit. Reaction of **7** with

Scheme 2

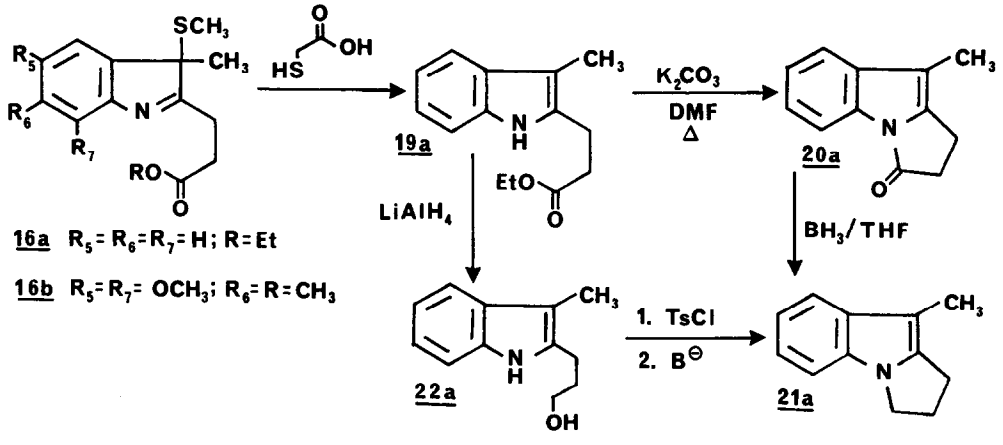


ethyl bromoacetate gave a mixture of C-acylation, **15**, and C-alkylation, **16a**, products in a 24:76 ratio. With methyl chloroacetate, in which the ester group reactivity is enhanced and S_N2 reactivity of the halide diminished relative to that expected for ethyl bromoacetate, only **17**, the product of C-acylation, was observed. With t-butyl bromoacetate, in which the ester group reactivity is diminished or with ethyl iodoacetate in which the S_N2 reactivity of the halide is enhanced, only **18** or **16** the product of C-alkylation was obtained. Reduction of the ester **16** with mercaptoacetic acid yielded the indole **19a** (65% overall yield from **5a**). Cyclization of **19a** was effected by heating with excess potassium carbonate in refluxing DMF for 30 minutes to yield **20a** (80% yield) which could be reduced to **21a** directly with borane/THF (98% yield). The pyrrolo [1,2-a]indole **21a** was also available by reduction of the ester **19a** to the alcohol **22a** (85% yield) followed by tosylation and base catalyzed cyclization (45% yield).[7]

Scheme 3

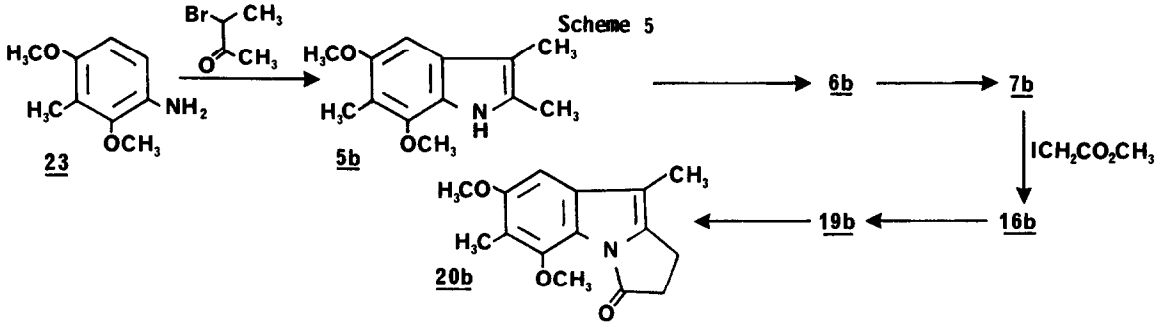


Scheme 4



The substituted system **20b** had been prepared previously by Kametani and coworkers[8] from the aniline **23** in thirteen steps (0.2% overall yield). Using the strategy outlined above, the indole **5b**, prepared by a Bischler-type reaction of the aniline **23**, was converted via **19b** to **20b** in four steps (24% overall yield from the aniline **23**).

Scheme 5



The availability of a substantial quantity of **20b** by this route makes further studies aimed at the conversion of this system to mitomycins and related compounds feasible and illustrates the potential value of side chain alkylation of 3-methylthioindolenines.

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2. P.G. Gassman, T.J. van Bergen, D.P. Gilbert, and B.W. Cue, Jr., J. Am. Chem.Soc. **1974**, 96, 5495.
3. R.W. Friesen, S.F. Vice, C.E. Findlay and G.I. Dmitrienko, Tetrahedron Lett. (preceding communication)
4. An additional potential advantage of the methodology outlined herein is that it is possible to perform the entire sequence as a "one pot" process. Thus, 2,3-dimethylindole was converted to 2-ethyl-3-methylindole in 95% yield by generating the 3-methylthioindolenine in anhydrous THF followed by deprotonation with two equivalents of LDA in THF, alkylation with methyl iodide and reduction with mercaptoacetic acid as compared with 65% yield by the stepwise approach. However, the "one pot" process was not uniformly successful since in some other instances the products could not be readily separated from minor impurities created in this approach.
6. For reviews of pyrrolo[1,2-a]indole synthesis and approaches to mitomycin antibiotics prior to 1979 see: (a) R.W. Franck, Prog. Chem. Org. Nat. Prod. **1979**, 38; (b) K. Takahashi and T. Kametani Heterocycles **1979**, 13, 411. For more recent approaches see J.R. Luly and H. Rapoport, J. Am. Chem. Soc. **1983**, 105, 2859 and R.M. Coates and P.A. MacManus J. Org. Chem., **1982**, 47, 4822 and references cited therein.
7. This compound has been prepared previously by a different route. See: A.S. Bailey, P.W. Scott and M.H. Vandervala, J. Chem. Soc. Perkin I **1980**, 97.
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