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INDOLOQUINONES FROM AZOMETHINE YLIDES VIA THE 4-OXAZOLINE ROUTE

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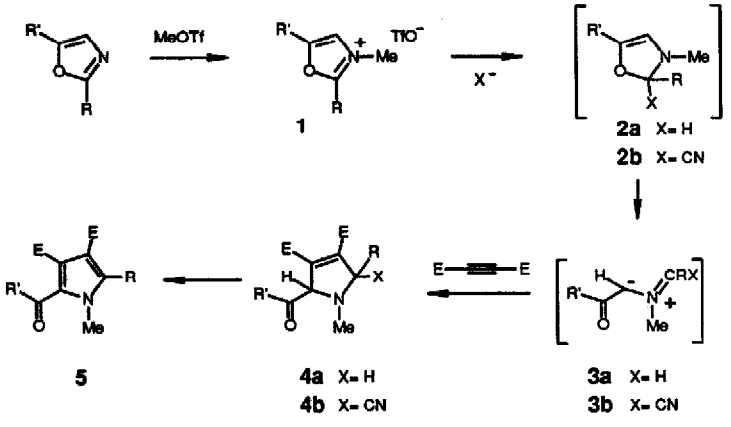
Summary. Internal trapping of the azomethine ylide **12** affords the bicyclic pyrrole **14** after deprotection. Further conversion of **14** into indoloquinone **17** is described.

Recent studies from this laboratory have reported access to stabilized azomethine ylides **3** via the electrocyclic ring opening of 4-oxazolines **2**.[1,2] The original version of this approach uses the controlled reduction of **1** to generate intermediate oxazolines **2a** and ylides **3a**. Trapping with dimethyl acetylenedicarboxylate followed by DDQ oxidation of adducts **4a** affords pyrroles **5**. A more recent variation of the above technique uses cyanide as the nucleophilic species that activates the oxazolium salt for ylide formation.[2] Thus, treatment of **1** with trimethylsilyl cyanide and cesium fluoride generates the labile oxazoline **2b**. After trapping of **3b** by 2+3 cycloaddition with an acetylenic dipolarophile, cyanide acts as the leaving group in the aromatization step from **4b** to **5**.[2]

Scheme 1.



We now report an application of the 4-oxazoline method for azomethine ylide generation to a concise synthesis of indoloquinones **6**, related in substitution to the indoloquinone subunit of the mitosenes.[3] Conceptually, the route resembles the Hershenson-Rebek adaptation of the Huisgen pyrrole synthesis where an intermolecular 2+3 cycloaddition was used.[3b] Our approach involves internal trapping of an azomethine ylide and results in simultaneous closure of the 6-membered as well as the 5-membered rings. As in previous illustrations of the intramolecular 2+3 cycloaddition using ylides generated from aziridines by pyrolysis,[4] internal trapping simplifies control of regiochemistry. In the present application, there are also advantages for the control of functionality and oxidation pattern.

The necessary oxazole starting material **7** was prepared in one step from 2-methylbutyrolactone according to the method of Jacobi.[5] Swern oxidation[6] gave the corresponding aldehyde **8**, and addition of $LiCCCO_2Et$ introduced the dipolarophilic triple bond and resulted in **9**. This reaction was troublesome, and a disappointing 28% yield was realized using the lithium propiolate anion[7] generated with butyllithium at low temperatures. However, the cerium-modified anion[8] proved more effective, and **9** could be obtained in 80% yield under carefully controlled conditions.[9]

Generation of the azomethine ylide **12** was performed after protection of **9** as the tert-butyldimethylsilyl ether **10** ($Me_2tBuSiOTf$/collidine/dichloromethane). In the first step, methylation with methyl triflate/acetonitrile gave the oxazolium salt **11** (not isolated). Next, the salt was combined with a 30% excess of Me_3SiCN and added to a suspension of anhydrous CsF in purified acetonitrile at reflux.[2,10] The initial product consisted of a mixture of **13** and **14**, but treatment with Bu_4NF prior to workup completed silyl ether cleavage and gave **14** in 68% yield.[11]

Final transformation into an indoloquinone could now be performed. An earlier model study had shown that the des-methyl analogue **15** is sensitive to aromatization to **16** in the presence of mineral acid. However, the undesired loss of C-4 oxygen did not occur under neutral conditions. Thus, **14** was treated with 2.4 moles of DDQ in toluene at reflux to afford the yellow-orange quinone **17** in >90% yield. None of the simple aromatization product was detected. The structure of **17** follows from the presence of characteristic NMR absorptions for the quinone and pyrrole protons, and other characteristic spectroscopic properties.[11,3c]

Further studies are in progress to define the scope of the indoloquinone synthesis.

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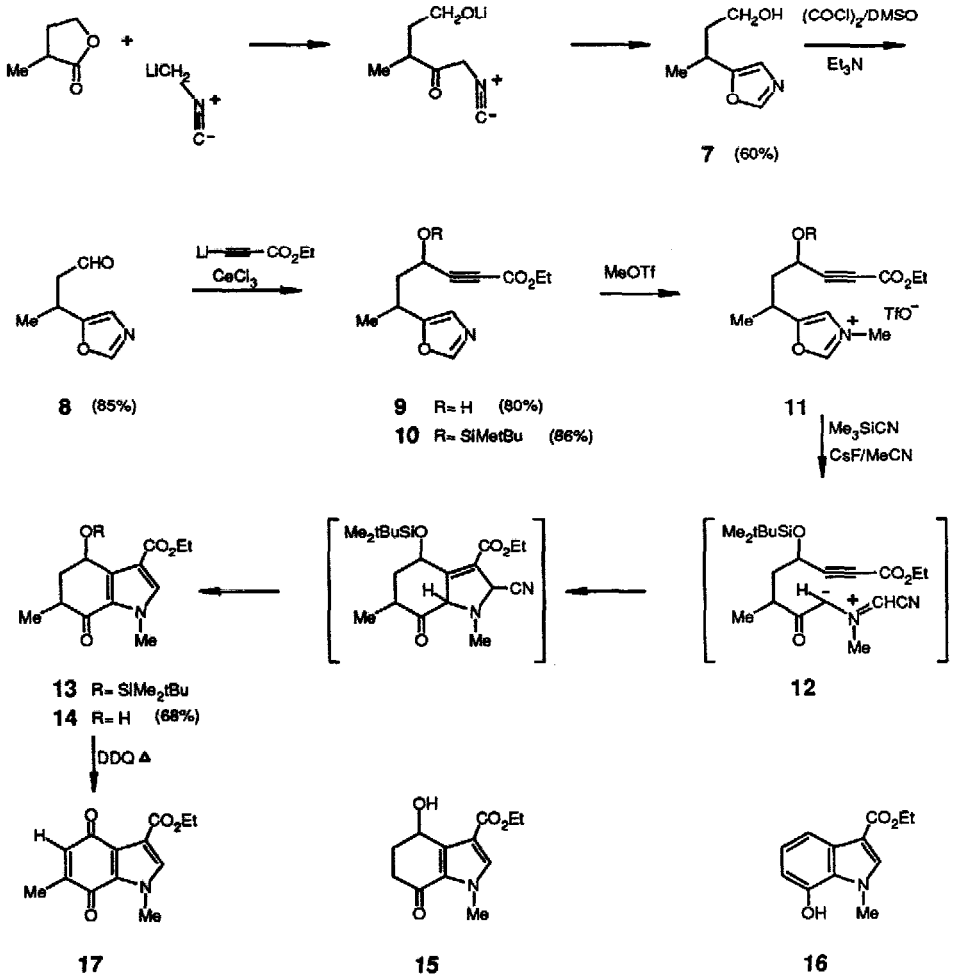
Scheme 2.


Me
LiCH2
CH2OLi
CH2OH
(COCl)2/DMSO
Et3N
7 (60%)
CHO
LiCeCl3
CO2Et
OR
MeOTf
TfO−
8 (85%)
9 R= H (80%)
10 R= SiMetBu (86%)
11
Me3SiCN
CsF/MeCN
Me2tBuSiO
CN
CHCN
12
13 R= SiMe2tBu
14 R= H (68%)
DDQ Δ
OH
15
16
17

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9. Butyllithium (3 mmol) in hexane was added dropwise to ethylpropiolate (3 mmol) in dry THF (6 mL) at -78 °C. After 30 min, the solution was added via a Dry-Ice packed cannula to anhydrous $CeCl_3$ suspended in dry THF with 2 h vigorous stirring at room temperature, and then cooled to -78 °C prior to addition of the anion. After 30 min stirring, the aldehyde **8** was added, the mixture was stirred for 45 min, and then quenched by the addition of aqueous ammonium chloride. Chromatographic purification gave the alcohol **9**, 80% yield.
10 Lower yields were obtained using the room temperature procedure described for the intermolecular examples of ref. 2.
11 Partial NMR data ($CDCl_3$, ppm); **14**: pyrrole C-H 7.34 (s), N-CH_3 3.92 (s); **17**: pyrrole C-H 7.38 (s), quinone C-H 6.48 (s), N-CH_3 3.98 (s), aryl-CH_3 2.05 (br s); IR ($CHCl_3$, cm^{-1}: 1740, 1660; all isolated intermediates gave satisfactory exact mass data.

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