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# USE OF N-LITHIATED ETHYL ANTHRANILATES AS 1,4-DIPOLE EQUIVALENTS IN 1,4-DIPOLE-ARYNE CYCLOADDITION: A NOVEL APPROACH TO THE SYNTHESIS OF ACRIDONES

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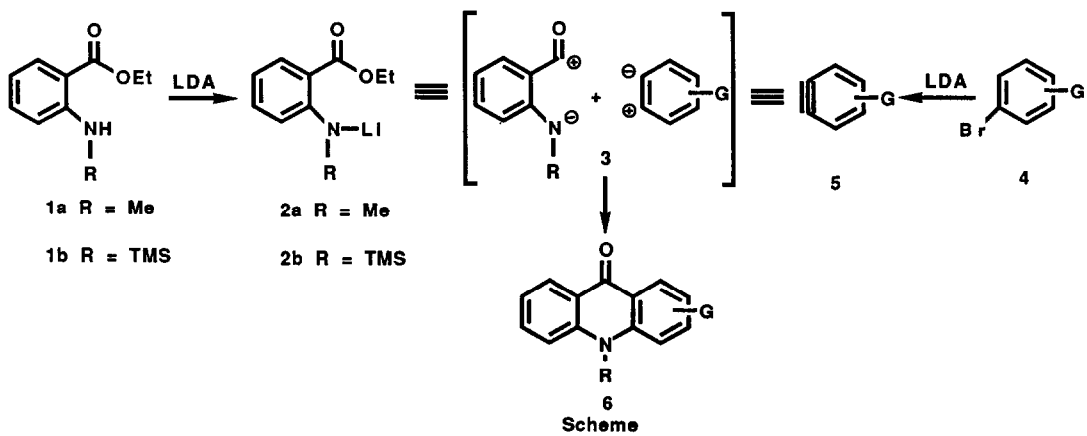
Abstract: A new strategy for acridones based on 1,4-dipolar cycloaddition of N-lithiated ethyl anthranilates, which function as 1,4-dipole equivalents, with arynes is reported.

Synthetic routes based on 1,4-dipolar cycloaddition have attracted much attention since they have resulted in convergent approaches for the construction of polycyclic systems under mild conditions. A number of reagents such as ortho phenyl substituted diesters[1], phthalide sulfones[2], phthalides[3], cyanophthalides[4], and ortho tolyl carboxylates[5] have been used as 1,4-dipole synthons. Our own efforts directed towards the 1,4-dipolar-aryne cycloaddition led us to develop convergent routes to anthraquinones[6], azaanthraquinones[7], and anthracyclinone intermediates.[8]

We now report the use of N-lithiated ethyl anthranilates (2) in 1,4-dipolar-aryne cycloadditions which proceed under mild conditions (-30 °C to 20 °C) to yield acridones. This reagent corresponds to a formal "1,4-dipole equivalent". The key feature of this strategy, which is outlined in the Scheme, involves the simultaneous formation of nitrogen-carbon and carbon-carbon bonds.

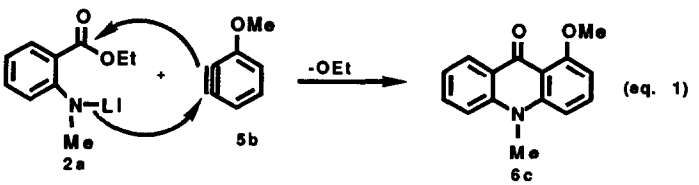



Scheme

Ethyl N-methylanthranilate (**1a** ) and ethyl N-(trimethylsilyl)anthranilate (**1b**) can be readily prepared[9] from ethyl anthranilate by metallation (n-BuLi) followed by quenching with either methyl iodide or trimethylsilylchloride.

In order to establish the utility of **2** as a 1,4-dipole equivalent, we investigated initially the cycloaddition of the N-methyl derivative (**2a**) with benzyne (**5a**, G = H) generated in situ from bromobenzene and found that N-methylacridone (**6a**) could be formed in good yield. In a typical procedure, LDA (10 mmol prepared in 30 mL THF) was added dropwise over 10 min to a solution of the N-methyl derivative **1a** (10 mmol in 40 ml of THF) at -78 °C. The solution was warmed to -20 °C over 1 h to yield an orange solution of the anion. The solution was cooled to -40 °C and bromobenzene (15 mmol in 30 ml THF) was added rapidly. Then LDA (20 mmol in 40 ml THF) was added dropwise, and the resulting solution was kept at -40 °C for 10 min, allowed to warm to room temperature, and quenched with aqueous saturated ammonium chloride solution. The usual work-up afforded a light yellow solid, which was washed with hexane/ether to give N-methylacridone in 71 % yield. Under similar conditions, the N-lithiated N-(trimethylsilyl) derivative **2b** afforded acridone (**6b**) in 42% yield. The TMS group was lost during the aqueous work-up.

Later, we found that 3-bromoanisole, 1-bromo-2,5-dimethoxybenzene, 1-bromo-2-iodo-4,5-(methylenedioxy)benzene, and 1-bromo-2-(methoxymethyl)-4,5-(methylenedioxy)benzene gave the corresponding acridones and N-methyl acridones in fair to moderate yields which are summarized in the Table. Three entries are worthy of note. First, the reaction of **2a** with 3-methoxybenzyne (**5b**, G = OMe) generated from 3-bromoanisole (entry 3) gave 1-methoxy-10-methylacridone (**6c**) as the exclusive aryne product (eq. 1). We have shown the regiocontrol in eq.1 as resulting from a concerted, non-synchronous cycloaddition of **2a** onto the polarized 3-aryne [10a] However, the regiocontrol could equally well arise by a non-concerted *cine* substitution, which has precedent in the anisole system.[10b]




Second, the symmetric 4,5-(methylenedioxy)benzyne intermediate **8** prepared from bromoiodoarene **7** and n-BuLi reacted with **2a** or **2b** to give (eq. 2) the respective 4-demethoxy or 4-deoxy analogs of the natural products evoxanthine[10] (**6g**) (entry 7) and evoxanthidine[11] (**6h**) (entry 8).

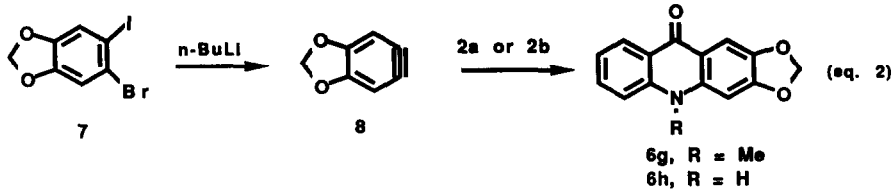
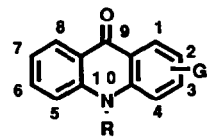



**Table: Yields and Melting Points of Acridones 6a-j[11]**



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| Entry | Compound | Yield, %[a] | m. p., °C |
|---|---|---|---|
| 1 | a. R = Me, G = H | 71 | 204-206 |
| 2 | b. R = G = H | 44 | > 340 (dec) |
| 3 | c. R = Me, G = 1-MeO | 57 | 161-162 |
| 4 | d. R = H, G = 1-MeO | 51 | 241-245 |
| 5 | e. R = H, G =1,4-di-MeO | 31 | 192-194 |
| 6 | f. R = Me, G = 1,2,3-tri-MeO | 58 | 146-149 (dec) |
| 7 | g. R = Me, G = 2,3-$OCH_2O$- | 47 | 189-191 (dec) |
| 8 | h. R = H, G = 2,3-$OCH_2O$- | 36 | > 300 (dec) |
| 9 | i. R = Me, G = 4-$CH_2OMe$, 1,2-$OCH_2O$- | 41[b] | 166-169 (dec) |

a. Isolated yields of pure product b. Product purified by chromatography over celite.

The importance of acridones to acridine chemistry can not be overstated since they provide ready access to this important class of tricyclic nitrogen heterocycles, which continue to find use in emerging areas of investigations. For example, 9-arylacridines[12] have been found to serve as rigid molecular tweezers.[13]

The most important methods for preparation of acridones[14] are 1) cyclization of diphenylamine-2-carboxylic acids, 2) cyclization of 2-amino-2'-fluorobenzophenones, and 3) pyrolysis of N-benzoylphenyl-amine-2-carboxylic acids. Other methods are available, but involve a multitude of steps.

Thus, we have developed a general, high yielding, simple approach to substituted acridones from readily-available ethyl anthranilates and haloarenes. To our knowledge, the N-lithiated anthranilates **1a** and **1b** represent the first examples of 1,4-dipole synthons possessing nitrogen. We are studying the application of

this method to the synthesis of important tumor inhibitors acronycine and noracronycine, and natural products, evoxanthine, evoxanthidine, norevoxanthine, mellicopidine and mellicopicine. The results will be reported in due course.

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9. Compounds **1a** and **1b** were prepared by metallation of ethyl anthranilate using 1.1 equiv of n-BuLi in THF at -78 °C. After the solutions were warmed to 0 °C then cooled to -78 °C , they were quenched with MeI or $(Me)_3SiCl$ and the THF was removed under vacuum. Pure **1a** was obtained by flash chromatography followed by distillation (b.p.120-122 °C @ 2.5 torr) in 49 % yield and pure **1b** was obtained by distillation (b. p. 114-118 °C @ 2.2 torr) in 96% yield.
10. a) See, for example: Gribble, G. W.; Keavy, D. J.; Branz, S. E.; Kelly, W. J.; Pals, M. A. Tetrahedron Lett. **1988**, 29, 6227. Pollart, D. J.; Rickborn, B. J. J. Org. Chem. **1987**, 52, 792. b) Roberts, J. D.; Simmons, H. E.; Carlsmith, L. A.; Vaughan, C. W. J. Am. Chem. Soc. **1953**, 75, 3290.
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