A NOVEL SYNTHESIS OF AZAACRIDONES USING 1,4-DIPOLAR ARYNE CYCLOADDITIONS

Subhash P. Khanapure, Baburao M. Bhawal, and Edward R. Biehl*
Department of Chemistry, Southern Methodist University, Dallas, Texas 75275, U.S.A.

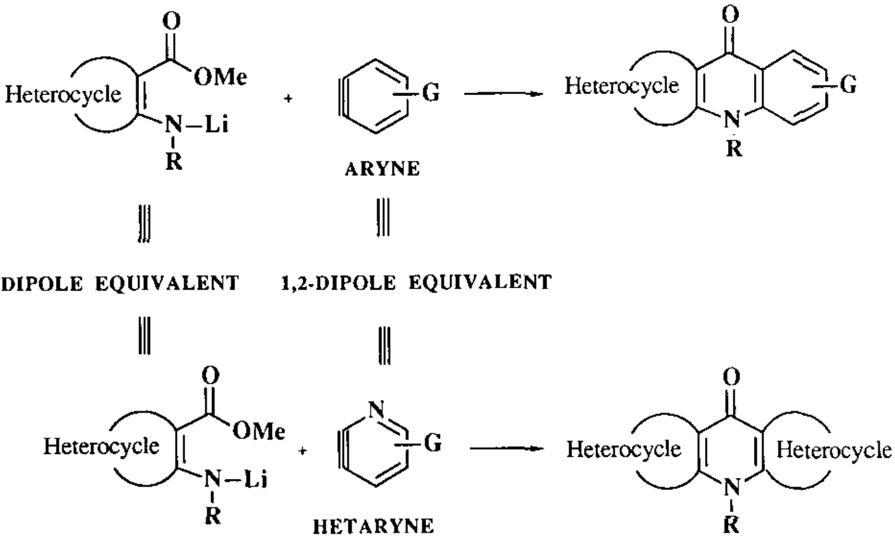
Abstract- A novel approach for the synthesis of azaacridones based on 1,4-dipolar cycloaddition of methyl N-lithiated 2-(aminotrimethylsilyl)nicotinate (**2a**) and methyl 3-(aminotrimethylsilyl)pyrazine-2-carboxylate (**2b**) which function as 1,4-dipole equivalents, with arynes is reported.

INTRODUCTION

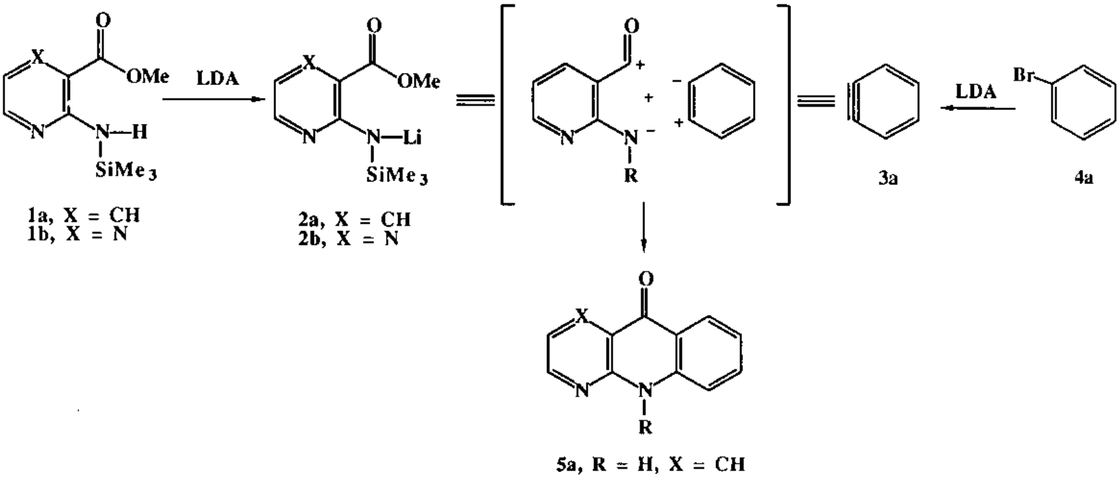
1,4-Dipolar cycloaddition reactions have attracted much attention since they provide convergent approaches for the construction of polycyclic systems under mild conditions.[1-8] Several reagents such as ortho-phenyl substituted diesters,[1] phthalide sulfones,[2] phthalides,[3] cyanophthalides,[4] and ortho-tolyl carboxylates[5] have been used as 1,4-dipole synthons. Using 1,4-dipolar-aryne cycloadditions we have developed convergent routes to anthraquinones,[6] azaanthraquinones,[7] and anthracyclinone intermediates.[8]

Watanabe and co-workers have done pioneering work in using methyl N-lithiated anthranilates in 1,4-dipolar-aryne cycloadditions which proceed under mild conditions to yield acridones.[9] These reagents correspond to formal "1,4-dipole equivalents". Based on this approach a novel synthesis of arconycine was reported.[9] Here we report the synthesis of novel azaacridones by similar methodology. The general strategy is outlined below.

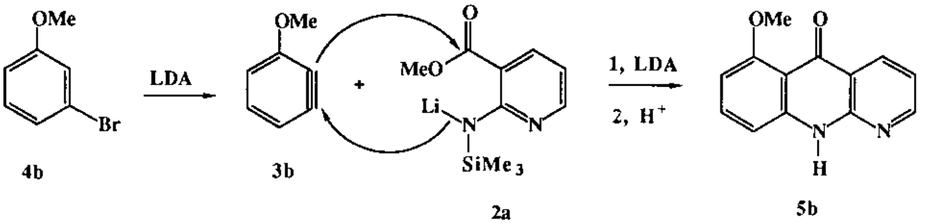
Scheme



The starting materials methyl 2-(aminotrimethylsilyl)nicotinate (**2a**) and methyl 3-(aminotrimethylsilyl)pyrazine-2-carboxylate (**2b**) can be readily prepared[10] from the coresponding amino methyl esters (**1a-b**) by metalation (n-BuLi) followed by quenching with trimethylsilyl chloride. We investigated initially, the cycloaddition of the N-silyl derivative (**2a**) with benzyne (**3a**) generated in situ from bromobenzene (**4a**) and found that 1-azaacridone (**5a**) could be obtained in 19% yield after aqueous work-up. The trimethylsilyl group was lost during the aqueous workup.



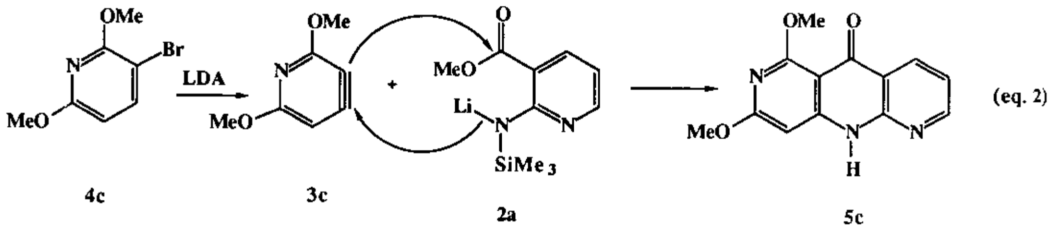
Later, we found that unsymmetric 3-methoxybenzyne (**3b**) generated from 3-bromoanisole (**4b**) reacted with **2b** to give the corresponding 6-methoxy-1-azaacridone (**5b**) in 46 % yields as the exclusive aryne product (eq. 1). The high degree of regioselectivity observed in this reaction indicates that the reaction involves a concerted, non-synchronous cycloaddition of **2a** onto the polarized 3-aryne (**3b**). Several investigators have recently observed similar unexpected regioselectivity in aryne cycloadditions with polarized arynes.[11]



(eq. 1)

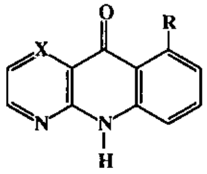
Under similar conditions 2,6-dimethoxy-3,4-didehydropyridyne (**3c**) generated from 3-bromo-2,6-dimethoxypyridine (**4c**) gave 5,7-dimethoxy-1,6-diazaacridone (**5c**) in 21 % yield (eq. 2). Later we studied the reactions of **2b** with haloarenes **4b** and **4c** to prepare 1,4-diaza- and 1,4,6-triazaacridones. The results are summerized in the Table.

Thus, we have developed a general and simple approach to substituted azaacridones and diazaacridones from readily-available methyl 2-(aminotrimethylsilyl)nicotinate (**2a**) and methyl 3-(aminotrimethylsilyl)pyrazine-2-carboxylate (**2b**), and haloarenes (**4a-c**).

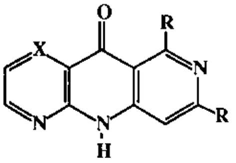


(eq. 2)

Table, yields of azaacridones



5a, X = CH, R = H
5b, X = CH, R = OCH $_3$
5d, X = N, R = OCH $_3$



5c, X = H, R = OCH $_3$
5e, X = N, R = OCH $_3$

Entry	N-silyl compound	Haloarene	Azaacridone	Yield (%)
1	**2a**	Bromobenzene (**4a**)	**5a**	**19**
2	**2a**	3-Bromoanisole (**4b**)	**5b**	**46**
3	**2a**	3-Bromo-2,6-dimethoxypyridine (**4c**)	**5c**	**21**
4	**2b**	**4b**	**5d**	**31**
5	**2b**	**4c**	**5e**	**27**

EXPERIMENTAL

In a typical procedure, LDA (5 mmol prepared in 15 ml of THF) was added dropwise over 10 min to a solution of the N-trimethylsilyl derivative (**2**) (5 mmol in 20 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 (7 mmol in 15 ml of THF) was added rapidly. Then LDA (10 mmol in 20 ml of 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 THF was evaporated under reduced pressure, and the residue was extracted with methylene chloride (2 x 50 ml). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated (rotary evaporator) to provide an oil which was treated with ether, the pure product was precipitated out as yellow needles, which was filtered off and washed with ether. All the azaacridones were obtained in pure form by treating the crude reaction mixture with ether and filtering the pure products obtained.

1-Azaacridone (5a): Yellow needles; mp 174-180 °C (decomp.) (ether); ^{1}H nmr ($CDCl_3$) δ 3.84 (s, 3H), 6.73 (d, J = 8.1 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.25 (m, 1H), 7.59 (t, J = 7.8 Hz, 1H), 8.44 (d, J = 7.9 Hz, 1H), 8.67 (m, 1H), 11.91 (br s, 1H); hrms, m / z observed (M^+) 196.0635, $C_{12}H_8N_2O$ requires 196.0635.

5-Methoxy-1-azaacridone (5b): Yellow needles; mp 207-210 °C (decomp.) (ether); ^{1}H nmr ($CDCl_3$) δ 3.84 (s, 3H), 6.73 (d, J = 8.1 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.25 (m, 1H), 7.59 (t, J = 7.8 Hz, 1H), 8.44 (d, J = 7.9 Hz, 1H), 8.67 (m, 1H), 11.91 (br s, 1H); hrms, m / z observed (M^+) 226.0742, $C_{13}H_{10}N_2O_2$ requires 226.0742.

5,7-Dimethoxy-1,6-diazaacridone (5c): Yellow needles; mp 189-197 °C (decomp.) (ether); ^{1}H nmr ($CDCl_3$) δ 3.90 (s, 3H), 3.96 (s, 3H),7.58 (m, 1H), 8.58-8.68 (m, 2H), 11.92 (br s, 1H); hrms, m / z observed (M^+) 257.0796, $C_{13}H_{11}N_3O_3$ requires 257.0796.

5-Methoxy-1,4-diazaacridone (5d): Yellow needles; mp 152-155 °C (decomp.) (ether); ^{1}H nmr ($CDCl_3$) δ 3.84 (s, 3H), 6.72 (d, J = 8.2 Hz, 1H), 7.23 (m, 2H), 7.59 (m, 1H), 8.42 (d, J = 7.6 Hz, 1H), 11.99 (br s, 1H); ms, m / z observed (M^+) 227.0692, $C_{12}H_9N_3O_2$ requires 227.0694.

5,7-Dimethoxy-1,4-diazaacridone (5e): Yellow needles; mp 198-205 °C (decomp.) (ether); ^{1}H nmr ($CDCl_3$) δ 3.90 (s, 3H), 3.96 (s, 3H), 6.37 (s, 1H), 7.59 (m, 1H), 11.99 (br s, 1H); ms, m / z 257 (M^+).

ACKNOWLEDGEMENTS

We thank the Robert Welch Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society for their generous financial support.

REFERENCES AND NOTES

1. a) W. Eisenmuth, H. B. Renfroe, and H. Schmid, Helv. Chim. Acta , **1965**, 48, 375. b) A. P. Kozikowski and R. Schmiesing, Synth. Commun., **1978**, 8, 363.
2. F. M. Hauser, S. Prasanna, and D. W. Combs, J. Org. Chem., **1983**, 48, 1328 and references therein.
3. N. J. Broom and P. G. Sammes, J. Chem. Soc., Chem. Commun., **1978**, 162.
4. a) G. A. Kraus and H. Sugimoto, Tetrahedron Lett., **1978**, 2263. b) T. Li and Y. Wu, J. Am. Chem. Soc., **1981**, 103, 7007. c) G. W. Morrow, J. S. Swenton, J. A. Filppi, and R. L. Wolgemuth, J. Org. Chem., **1987**, 52, 713 and references therein.
5. J. H. Dodd and S. M. Weinreb, Tetrahedron Lett., **1979**, 3593.
6. S. P. Khanapure, T. R. Reddy, and E. R. Biehl, J. Org. Chem., **1987**, 52, 5685.
7. a) S. P. Khanapure and E. R. Biehl, Heterocycles, **1988**, 27, 2643. b) S. P. Khanapure and E. R. Biehl, J. Nat. Prod., **1989**, 52, 1357.
8. S. P. Khanapure and E. R. Biehl, Synthesis, **1991**, 33.
9. M. Watanabe, A. Kurusaki, and S. Furukawa, Chem. Pharm. Bull., **1984**, 32, 1264.
10. Compounds (**2a**)and (**2b**)were prepared by metalation of methyl 2-aminonicotinate and methyl 3-aminopyrazine -2-carboxylate respectively 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 $(CH_3)_3SiCl$ and the THF was removed under vacuum. Pure **2a** and **2b** were obtained by kugelrohr distillation (**2a**, bp 120-122 °C / 0.5 torr, in 89 % yield), (**2b**, bp 124-128 °C / 0.2 torr, in 98% yield).
11. For examples of unanticipated regioselective Diels-Alder aryne cycloadditions see: a) G. W. Gribble, D. J. Keavy, S. E. Branz, W. J. Kelly, and M. A. Pals, Tetrahedron Lett., **1988**, 29, 6227. b) D. J. Pollart and B. J. Rickborn, J. Org. Chem., **1987**, 52, 792 and references therein.

Received, 7th June, 1991