Supplementary Material Available: Experimental details for the compounds in this paper (10 pages). Ordering information is given on any current masthead page.

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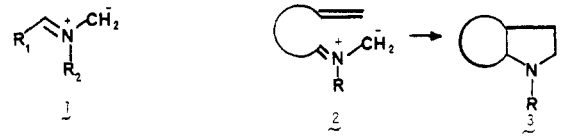
An Expedient Synthetic Approach to the Physostigmine Alkaloids via Intramolecular Formamidine Ylide Cycloadditions

Summary: New approaches for the direct generation of several highly reactive imidate methylides are described that rely upon acyl fluoride mediated desilylation. The utility of this methodology has been demonstrated in a stereospecific synthesis of *dl*-eserethole (**4**), which embodies the first example of an intramolecular dipolar addition of a formamidine ylide to an *unactivated* olefin as a central feature.

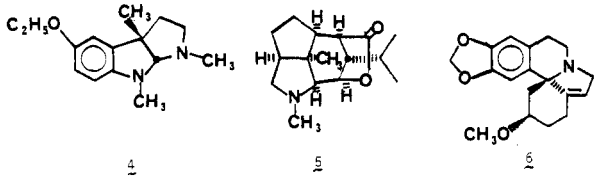
Sir: The prominent role that 1,3-dipolar cycloaddition reactions play in the elaboration of a variety of heterocycles has become increasingly apparent in recent years. The vast majority of studies bearing relevance to natural product synthesis have hinged upon the utilization of "classical" dipoles (as exemplified by nitrones, azomethine imines, and nitrile oxides).

Accounts concerned with the generation and subsequent 1,3-dipolar addition reactions of nonstabilized azomethine ylides (e.g., **1**) have, by comparison, remained relatively



R_1 = alkyl, RS-, R_2N-

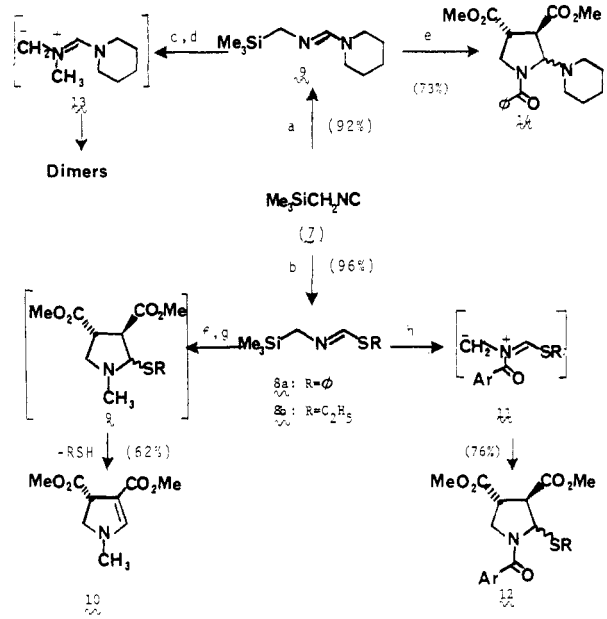
R_2 = alkyl



few in number.[1,2] In principle, the use of these species in intramolecular cyclization reactions (e.g., **2** → **3**) should facilitate efficient synthetic approaches to numerous naturally occurring alkaloids. Several representative examples include eserethole (**4**), dendrobine (**5**), and erythramine (**6**), in addition to alkaloids belonging to the dendrobatid and amarylidaceae groups.

The purpose of this communication is to report our observations on the utility and limitations exhibited by formamidine methylides, e.g., **1** (R_1 = R_2N), and thioformimidate methylides, e.g., **1** (R_1 = RS), as synthetic intermediates. In addition, we describe the first example of an *intramolecular* dipolar addition of a nonstabilized azomethine ylide to an appropriately situated olefin. Moreover, in contrast to their intermolecular counterparts, we have found that these cyclizations proceed efficiently with *unactivated* olefins.

Reports from several laboratories have disclosed the ability of organic isonitriles to enter into a diverse array of synthetic transformations. Of these, we have found the copper-mediated insertion reactions of protic nucleophiles[3] with **7** to be the most useful.[4] Treatment of isonitrile[5] **7**



(a) $C_5H_{10}NH$, CuCl. (b) RSH, $Cu(acac)_2$. (c) CH_3I. (d) CsF. (e) PhCO-F, $MeO_2CCH{:}CHCO_2Me$. (f) CH_3I. (g) CsF, $MeO_2CCH{:}CHCO_2Me$. (h) p-O_2N-C_6H_4COF, $MeO_2CCH{:}CHCO_2Me$, CH_3CN.

with thiophenol (1 equiv, 50 °C, 3 h) in the presence of a catalytic amount of $Cu(acac)_2$ furnished the anticipated thioformimidate **8a** in 96% yield. Similarily, exposure of **7** to piperidine (2 equiv, 110 °C, 2 h) and a catalytic quantity of Cu_2Cl_2 afforded the formamidine **9** (92%). In contrast to these observations, the reaction of **7** with a variety of alcohols under similar reaction conditions invariably resulted in desilylation of the isonitrile.

The conversion of thioformimidates such as **8** to the corresponding dipolar methylides is experimentally straightforward as illustrated by the following examples. Alkylation of **8a** with iodomethane (1 equiv) in CH_3CN at 25 °C (16 h) followed by the addition of dimethyl fumarate (1 equiv) and CsF (2.5 equiv) afforded the pyrroline **10** in 62% yield.[6] Alternatively, exposure of **8b** in CH_3CN to

(1) For an interesting recent example of pertinence to this communication, see: Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1980** *102*, 7993 and references therein.

(2) Terao, Y.; Imai, N.; Achiwa, K.; Sekiya, M. *Chem. Pharm. Bull.* **1982**, *30*, 3167.

(3) Saegusa, T.; Kobayashi, S.; Hirota, K.; Okamura, Y.; Iro, Y. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1638.

(4) An additional mode of isonitrile functionalization that imparts enhanced flexibility to the methodology described in this communication involves the alkylation of the lithio derivative corresponding to **7**. Schollkopf, U.; Jentch, R.; Madawinta, K.; Harms, R. *Justus Liebigs Ann. Chem.* **1976**, 2105.

(5) Smith, R.; Livinghouse, T. *J. Chem. Soc., Chem. Commun.*, in press.

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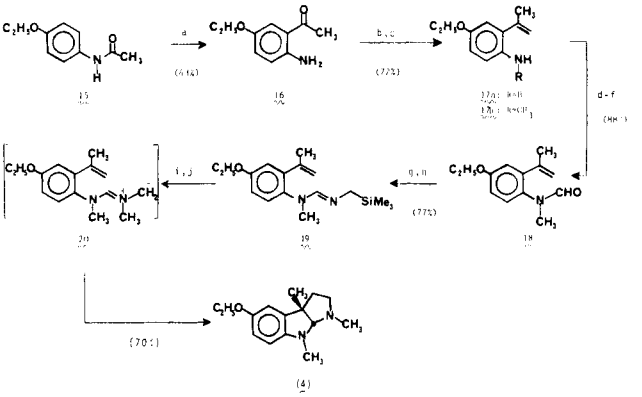
p-nitrobenzoyl fluoride (1 equiv) in the presence of dimethyl fumarate (1 equiv, 65 °C, 3 h) furnished the pyrrolidines **12** in 76% yield.[7] In our experience the acyl fluoride mediated generation of substituted thioformimidate methylides frequently offers advantages over the alkylative approach.[8,9] This distinction becomes even more dramatic in the generation and subsequent intermolecular trapping of dipolar ylides derived from silylated formamidines. Numerous efforts to intercept the methylide **13** formed via sequential methylation[3]–desilylation of the formamidine **9** under a variety of experimental conditions resulted in the formation of intractable products. However, slow addition of benzoyl fluoride (1 equiv) to a mixture of **9** and dimethyl fumarate (1 equiv) in CH_3CN at 65 °C (3 h) provided the pyrrolidine **14** as a mixture of epimers in 73% yield.[10]

In contrast to these findings, efforts to trap the dipoles **11** and **13** with less reactive dipolarophiles (e.g., phenylacetylene or 1-pentyne) have met with limited success.

Regardless of the merits and limitations observed in the foregoing examples, it became apparent that the application of this methodology in an intramolecular context (e.g., **2** → **3**) deserved exploration. The neurotoxic physostigmine alkaloid eserethole (**4**)[11] appeared an attractive initial target to test the viability of this concept. Irradiation of *p*-ethoxyacetanilide (**15**) in acetonitrile (2537 Å) furnished the aminoacetophenone **16** in 43% yield. Exposure of **16** to methyllithium (2 equiv, 0–25 °C, 30 min) followed by thermal dehydration at 250 °C gave the aminostyrene **17a** (72% overall). Sequential formylation of **17a** (C_4H_9OCHO, 108 °C, 72 h) followed by N-methylation [NaH (1 equiv), then CH_3I (1 equiv), xylene reflux] afforded formamide **18** (88%).[12] Treatment of **18** with



(a) 254 nm, CH_3CN. (b) CH_3Li. (c) 250°, $-H_2O$. (d) $BuOCHO$. (e) NaH. (f) CH_3I. (g) CH_3OTf. (h) $Me_3SiCH_2NH_2$. (i) CH_3OTf. (j) $Bu_4N^+F^-$.

methyl trifluoromethanesulfonate (1.1 equiv) and subsequent amination ($Me_3SiCH_2NH_2$, 1.15 equiv, 0 °C, CH_2Cl_2) provided the formamidine **19** (77%). Final cyclization of **19** to *d,l*-eserethole (**4**) via the transient ylide **20** was readily accomplished by sequential methylation ($CH_3O_3SCF_3$, 25 °C, CH_2Cl_2) and desilylation ($Bu_4N^+F^-$, 45 °C, THF)[13,14] in 70% overall yield.[15]

It is hoped that this general approach to the synthesis of the pyrrolidine ring systems of the physostigmine alkaloids will prove sufficiently flexible for the construction of other naturally occurring ring systems. Investigations directed toward this objective are in progress.

Acknowledgment. Support from the Research Corporation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

Registry No. (±)-**4**, 69926-96-1; **8a**, 85236-99-3; **8b**, 85237-01-0; **9** (R = Ph), 85237-04-3; (±)-**10**, 85237-00-9; (±)-**12** (R = Et; Ar = *p*-$NO_2C_6H_4$) (isomer 1), 85237-02-1; (±)-**12** (R = Et; Ar = *p*-$NO_2C_6H_4$) (isomer 2), 85237-03-2; (±)-**14** (isomer 1), 85237-05-4; (±)-**14** (isomer 2), 85237-09-8; **15**, 62-44-2; **16**, 42465-57-6; **17a**, 85237-06-5; **18**, 85237-07-6; **19**, 85237-08-7; dimethyl fumarate, 624-49-7; *p*-nitrobenzoyl fluoride, 403-50-9; benzoyl fluoride, 455-32-3.

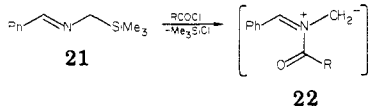
(6) (a) Satisfactory spectral and elemental analyses were obtained on all new compounds reported. All reported yields refer to distilled or chromatographed products. (b) Spectral characteristics for several representitive compounds are as follows. Pyrroline **10**: ^1H NMR δ 2.41 (1 H, m, CH), 2.82 (3 H, s, CH_3), 3.25 (2 H, m, CH_2), 3.60 (3 H, s, CH_3), 3.69 (3 H, s, CH_3), 7.03 (1 H, s, vinyl CH); IR (film) 2985–2760 (CH), 1745 (C=O), 1709 (C=O). Pyrrolidine **12**: ^1H NMR δ 1.26 (3 H, t, J = 8.08 Hz, CH_3), 2.59 (2 H, q, J = 8.08 Hz, CH_2), 2.76 (2 H, m, 2CH), 3.47 (2 H, m, CH_2), 3.69 (3 H, s, CH_3), 3.75 (3 H, s, CH_3), 5.33 (1 H, m, CH), 7.70 (2 H, d, J = 10.35 Hz, aromatic CH), 8.26 (2 H, d, J = 10.35 Hz, aromatic CH); IR (film) 2954–2810 (CH), 1742 (CO), 1645 cm^{-1} (CO). Pyrrolidine **14**: ^1H NMR δ 1.45–1.85 (6 H, methylene envelope, CH_2), 3.12–3.39 (4 H, methylene envelope, CH_2), 3.53 (2 H, m, CH_2), 3.68 (3 H, s, CH_3), 3.74 (3 H, s, CH_3), 5.25 (1 H, m, CH), 7.39 (3 H, m, aromatic CH), 7.77 (2 H, m, aromatic CH); IR (film) 2952–2790 (CH), 1741 (CO), 1711 (CO), 1665 cm^{-1} (CO). Formamidine **9**: ^1H NMR δ 0.09 (9 H, s, CH_3), 1.51 (6 H, m, $3CH_2$), 2.81 (2 H, s, CH_2), 3.12 (4 H, m, CH_2), 7.06 (1 H, s, CH); IR (film) 2970–2760 (CH), 1640 cm^{-1} (C=N). Formamidine **19**: ^1H NMR δ 0.09 (9 H, s, CH_3), 1.32 (3 H, t, J = 7.57 Hz, CH_3), 1.83 (3 H s, CH_3), 2.80 (2 H, s, CH_2), 3.0 (3 H, s, CH_3), 3.88 (2 H, q, J = 7.57 Hz, CH_2), 4.86 (1 H, m, vinyl CH), 4.98 (1 H, m, vinyl CH), 6.75 (2 H, m, aromatic CH), 7.22 (1 H, m, aromatic CH), 7.98 (1 H, s, CH); IR (film) 3080–2740 (CH), 1640 cm^{-1} (C=N).

(7) The trans-trans/trans-cis ratio of the product pyrrolidines was determined to be approximately 3:7 by NMR integration.

(8) Substitution of acyl chlorides for acyl fluorides in the reactions affords only poor yields of cyclized products.

(9) A more detailed account of our findings on the reaction of silylated imines, formamidines, and thioformimidates will be reported in due course.

(10) Recently, Achiwa and Sekiya (Achiwa, K.; Sekiya, M. (*Chem. Lett.* **1981**, 1213) have reported that acyl chlorides are capable of converting the imine **21** to *N*-acylmethylides (e.g., **22**). Efforts in our laboratories to convert the thioformimidate **8b** the formamidine **9** or (trimethylsily)methylimines other than **21** to the corresponding azomethine ylides under *these* conditions have been unsuccessful.



21 22

(11) For a pertinent review of the isolation, chemistry, and pharmacology of these alkaloids, see: Robinson, B. *Alkaloids* (*N.Y.*) **1968**, *10*, 383.

(12) Efforts to obtain formamidine **19** directly by treating the aminosytrene **17b** with the isonitrile **7** in the presence of cuprous chloride have shown limited promise.

(13) The following represents a typical experiment procedure: An oven-dried 5-mL round-bottom flask, equipped with a magnetic stirring bar, was charged with 6.45 of tetra-*n*-butylammonium fluoride (1.72 mmol), 2 mL of dry tetrahydrofuran, and 4-Å molecular sieves. The flask was flushed with nitrogen, stoppered with a serum cap, and heated to 50 °C. Formamidine **19** (83 mg, 0.273 mmol) was methylated with 1.15 equiv of methyl trifluoromethanesulfonate (25 °C, 16 h) and subsequently taken up in 0.75 mL of glyme. The resulting solution was added via syringe drive[12] to the tetra-*n*-butylammonium fluoride solution over 3.5. The reaction mixture was stirred at 50 °C for 12 h and was subsequently treated with saturated potassium carbonate and extracted with ether. The organic extract was washed with water and brine. The organic solvents were removed in vacuo, and the residue was submitted to chromotography on a column of silica gel (5% methanol chloroform for elution). A yellow oil (47 mg, 70% yield) was obtained on concentration of the pure fractions followed by evaporative distillation at 0.002 torr.[15]

(14) It is essential to employ inverse addition of the formamidinium trifluoromethanesulfonate salt formed in this manner via mechanical syringe (4 h) to anhydrous tetra-*N*-butylammonium fluoride (2.5 equiv) to tetrahydrofuran containing 4-Å molecular sieves to obtain the indicated yield.

(15) The synthetic *d,l*-eserethole prepared in this manner was identical in all respects (C^{13} resonance spectrum, TLC, and 300-MHz proton resonance spectrum) with an authentic sample of l-(−)-eserethole.

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