Acknowledgment. This work was supported by the NSF (CHE 82-00049). K.P.C.V. was a Camille and Henry Dreyfus Teacher-Scholar (1978-1983).

Registry No. (±)-**1**, 31456-25-4; **3**, 12078-25-0; **4**, 871-84-1; **5**, 103-71-9; **6**, 92957-80-7; **7**, 2396-63-6; **8**, 1943-82-4; **9**, 92957-81-8; **10**, 1295-35-8; **11**, 622-76-4; **12**, 92957-82-9; **13**, 92957-83-0; **14**, 92957-84-1; **26a**, 88761-58-4; **26b**, 88761-62-0; **27a**, 14630-40-1; **27b**, 18270-17-2; **27c**, 88761-61-9; **27c** (ketone), 18387-58-1; **27d**, 14630-42-3; **27e**, 35792-10-0; **27e** (ketone), 1679-36-3; **27f**, 88761-60-8; **27g**, 4341-76-8; **28**, 53293-00-8; **29**, 55183-45-4; **30**, 88761-32-4; **31**, 88761-33-5; **32**, 88761-35-7; **33**, 88761-42-6; **34**, 92957-85-2; **35**, 92957-86-3; **36**, 88761-43-7; **37**, 88761-44-8; **38**, 92957-88-5; **39**, 92957-89-6; **40**, 92958-08-2; **41**, 92957-91-0; **42**, 92957-87-4; **49**, 63281-84-5; **51**, 1490-25-1; **52**, 88761-59-5; **53**, 92958-07-1; **55**, 92957-90-9; **56**, 88761-45-9; **57**, 88761-48-2; **58**, 88761-49-3; **59**, 88761-51-7; **60**, 88761-50-6; **61**, 50478-69-8; **62**, 88761-54-0; **63**, 92957-92-1; **64**, 92957-93-2; **65**, 92957-94-3; **66**, 88761-36-8; **67**, 92957-95-4; **68**, 92957-96-5; **69**, 92957-97-6; **70**, 88761-39-1; **71**, 88761-37-9; **72**, 92957-98-7; **73**, 88761-47-1; **74**, 88761-46-0; **75**, 92957-99-8; **76**, 88761-53-9; **77**, 88761-56-2; **78**, 88761-55-1; **79**, 88761-52-8; **80**, 92958-00-4; **81**, 92958-01-5; **82**, 92958-02-6; **84**, 92958-03-7; **85**, 64389-33-9; **86**, 92958-04-8; **87**, 92958-05-9; **88**, 92958-06-0; $HC{\equiv}C(CH_2)_4OH$, 928-90-5; *t*-BuC≡CH, 917-92-0; Me_3SiCl, 75-77-4; *n*-PrC≡CCH_2OH, 764-60-3; TBDPSCl, 58479-61-1; $CH_2{=}N(CH_3)_2{}^+Cl^-$, 30354-18-8; PhC≡CH, 536-74-3; CuI, 7681-65-4; $PdCl_2(PhCN)_2$, 14420-64-5; $CH_2{=}CHCO_2Me$, 96-33-3; $PhCH{=}CH_2$, 100-42-5; $(EtO)_2CO$, 105-58-8; *N*-(2-aminobenzylidene)-*p*-toluidine, 55857-35-7.

(73) Quick, J. Ph.D. Thesis, University of Pittsburgh, 1972.
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Utility of *p*-Nitrophenyl 3-Bromo-2,2-diethoxypropionate (NPBDP) in Heterocyclic Synthesis

John L. LaMattina* and Christian J. Mularski

Central Research, Pfizer Inc., Groton, Connecticut 06340

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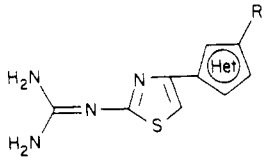
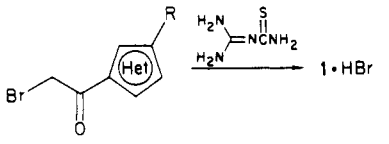
p-Nitrophenyl 3-bromo-2,2-diethoxypropionate (NPBDP, **3**) reacts with a variety of nucleophiles at the activated ester to afford the corresponding 3-bromo-2,2-diethoxypropionylated derivatives. With bifunctional nucleophiles, propionylation can be followed by intramolecular cyclization to give cyclic products. The α-bromo ketone moiety of the propionylated derivative can be liberated by heating at 85 °C in 95% formic acid. The utility of NPBDP in the synthesis of highly functionalized small molecules, as well as heterocycles, is presented.

Work from these laboratories designed to discover novel therapeutic agents led to the identification of an interesting series of 2-guanidino-4-(heteroaryl)thiazoles of general structure **1**, in which the heteroaryl ring was a five-membered nitrogen containing ring. The original syntheses of **1** were cumbersome, in that they were based on building a heterocycle onto a preformed 2-guanidinothiazole moiety. While this approach proved suitable for the initial targets, the preparation of other derivatives of interest was difficult because of the general insolubility of guanidinothiazoles, a characteristic attributable to their propensity for hydrogen bonding.



1

Pursuant to the activity of **1**, it was of interest to prepare compounds in which the heteroaryl ring was a 5-(1,2,4-oxadiazolyl) and 5-(1,2,4-thiadiazolyl) moiety. It was also desirable to replace the 2-guanidinothiazole with a 5-guanidino-1,2,4-oxadiazole. Both of these goals were either difficult or precluded by the original synthesis, and thus, an alternate scheme was necessary. A route that was especially appealing involved forming the 2-guanidinothiazole moiety in the last step so that the very characteristics which cause the insolubility of these compounds could be used to facilitate their isolation in pure form. However, in order for such a scheme to be successful, a simple synthesis of the appropriate 2-halo-1-heteroaryl-1-ethanones (**2**) was necessary. This paper details reactions of *p*-nitrophenyl 3-bromo-2,2-diethoxypropionate (NPBDP, **3**), a reagent which proved to be ideally suited to the preparation of these key ethanones. Also presented are reactions that demonstrate the utility of NPBDP, not only in heterocyclic synthesis but also in the synthesis of highly functionalized small molecules.[1]



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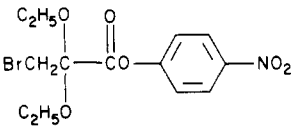


NPBDP

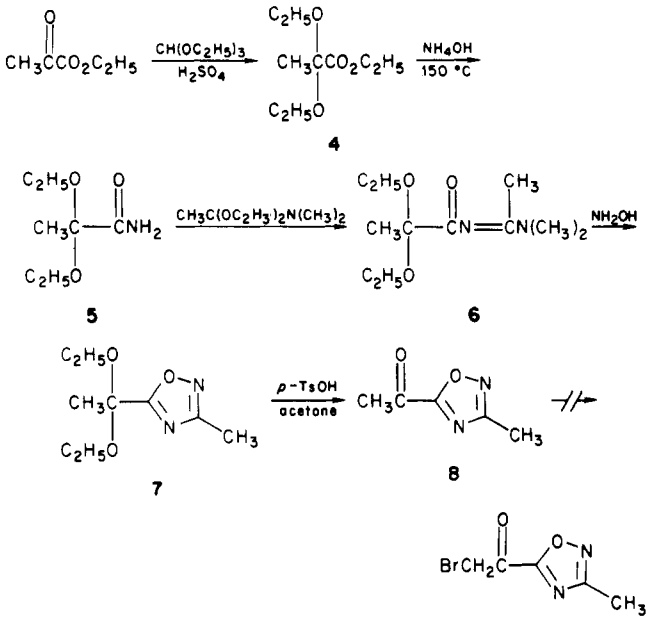
3

The necessity of a reagent such as NPBDP for these purposes is best demonstrated by the initial unsuccessful attempts at preparing a 5-(1,2,4-oxadiazolyl) analogue of **1**. This approach was based on recent chemistry developed by Lin et al.[2] Ethyl pyruvate was converted to ketal **4**, which, when treated with ammonium hydroxide, gave 2,2-diethoxypropionamide (**5**). Reaction of **5** with dimethylacetamide dimethyl acetal readily gave amidine **6**, which, upon reaction with hydroxylamine followed by

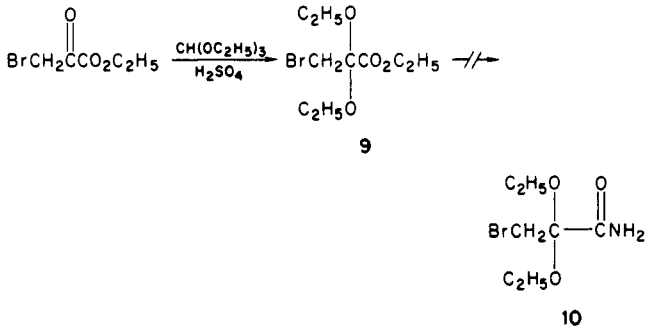
(1) For a preliminary account of this work, see: LaMattina, J. L.; Mularski, C. J. *Tetrahedron Lett.*, **1983**, 2059.
(2) Lin, Y.; Lang, S. A., Jr.; Lovell, M. F.; Perkinson, N. A. *J. Org. Chem.* **1979**, *44*, 4160.

0022-3263/84/1949-4800$01.50/0

treatment with acetic acid, gave 5-(1,1-diethoxyethyl)-3-methyl-1,2,4-oxadiazole (7). Deprotection of the ketone using *p*-toluenesulfonic acid (*p*-TsOH) in acetone gave 8. Unfortunately, all attempts to convert 8 to its α-bromo ketone failed. In general, mild conditions resulted in no reaction, whereas more vigorous conditions resulted in concomitant destruction of the heterocyclic ring.

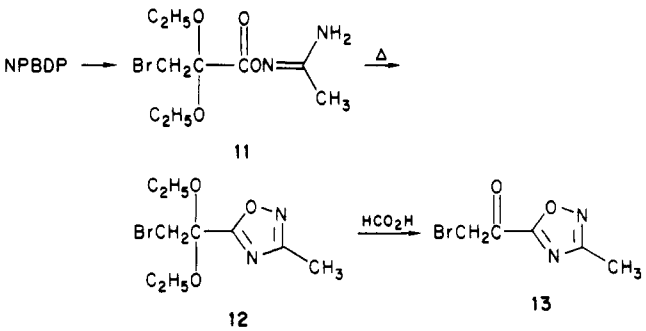


It was clear that the bromo moiety had to be incorporated at an earlier stage in the synthesis. Thus, ethyl bromopyruvate was converted to its ketal 9. However, all attempts to convert 9 to 3-bromo-2,2-diethoxypropionamide (10) failed.

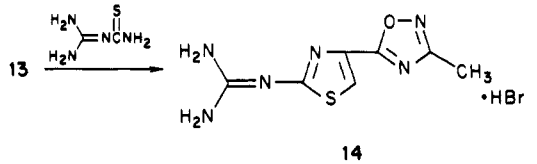


It became apparent that in redesigning a synthesis of the desired analogues, a synthon was required that possessed two of the more general precursors of five-membered heterocyclic rings, i.e., an α-halo ketone and an activated carboxylic acid. Such a molecule would contain, in effect, three contiguous electropositive carbon atoms. Clearly, this molecule must be carefully designed so that chemoselective control can be realized in its reaction with nucleophiles. NPBDP was developed to meet these criteria. Its neopentyl-like structure should hinder nucleophilic attack at the α-bromo carbon atom, thus resulting in nucleophiles reacting exclusively at the active ester. Subsequent elaboration of the carboxylic moiety, followed by unmasking of the carbonyl, should afford the desired 2-bromo-1-heteroaryl-1-ethanone. This has been found to be the case.

Treatment of NPBDP with acetamidoxime yielded adduct 11, exclusively. Cyclization of 11 with *p*-toluenesulfonic acid in refluxing toluene afforded 1,2,4-oxadiazole 12. Surprisingly, deketalization of 12 proved difficult. Mild conditions, such as *p*-toluenesulfonic acid/acetone, resulted in no reaction as did reaction of 12 with dilute aqueous hydrobromic acid at room temperature. Upon warming in dilute mineral acids, decomposition of 12 occurred. This resistance to deketalization is probably due to the difficulty in generating a carbonium ion that is flanked by two electropositive centers. This is substantiated, in part, by the aforementioned deketalization of 5-(1,1-diethoxyethyl)-3-methyl-1,2,4-oxadiazole (7), which occurred readily, since in this case, the incipient carbonium ion is flanked by only one electropositive center. Deketalization of 12 was finally realized by using 98% formic acid at 85 °C to give the desired α-bromo ketone 13. The success of formic acid can be attributed to the fact that it is a strong enough acid to allow deketalization but not potent enough to rupture the 1,2,4-oxadiazole ring.[3]



Conversion of 13 to the desired 2-guanidinothiazole 14 readily occurred with amidinothiourea in refluxing acetone. It is important to note that under these conditions, pure 14 precipitates during the reaction as its hydrobromide salt. This method of synthesis therefore takes advantage of the solubility properties of 2-guanidinothiazoles by generating this moiety in the final step, thereby facilitating isolation of the product.



In order to prepare an analogous 1,2,4-thiadiazole derivative, 3-bromo-2,2-diethoxythiopropionamide (15) was required. Reaction of NPBDP with ammonia in tetrahydrofuran at room temperature immediately affords 3-bromo-2,2-diethoxypropionamide (10), a compound which was earlier shown to be inaccessible from ethyl bromopyruvate. Direct conversions of amide 10 to 15 using either P_2S_5 or Lawesson's Reagent[4] failed. A two-step sequence involving 3-bromo-2,2-diethoxypropionitrile (16) was next explored. Treatment of 10 with trifluoroacetic anhydride/pyridine[5] afforded 16. Conversion of 16 to thioamide 15 using standard conditions (thioacetamide, DMF, HBr)[6] failed, probably because of the strong acid conditions required. However, Benner's method[7] which employs very mild conditions (Ph_2PS_2H, 2-propanol, 40 °C), gave reasonable yields of 15.

The reaction of 15 with dimethylformamide dimethyl acetal yielded the expected amidine 17. Treatment of 17

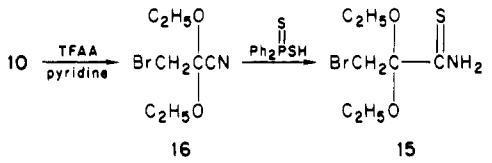
(3) The hydrolysis of α-ketoacetals, another system in which the required carbonium ion is destablized by a neighboring electropositive center, has been shown to be difficult: Petrakis, K. S.; Fried, *J. Synthesis* **1983**, 891.

(4) Pedersen, B. S.; Scheibye, S.; Nilsson, N. H.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 223.

(5) Campagna, F.; Carotti, A.; Casini, G. *Tetrahedron Lett.* **1977**, 1813.

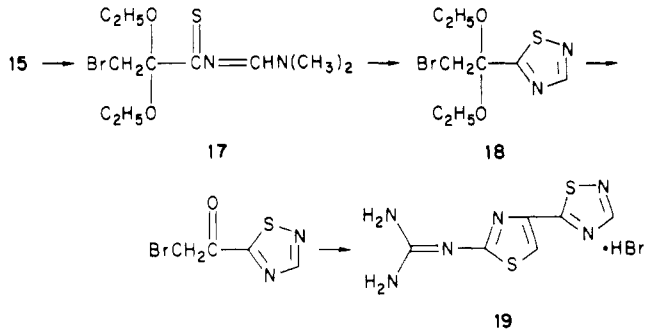
(6) Taylor, E. C.; Zoltewicz, J. A. *J. Am. Chem. Soc.* **1960**, *82*, 2656.

(7) Benner, S. A. *Tetrahedron Lett.* **1981**, 1851.



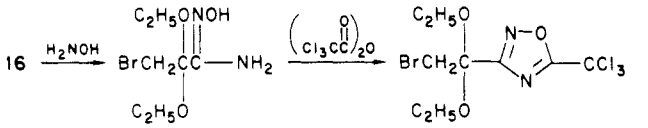
16 15

with hydroxylamine *O*-sulfonic acid gave 77% of the 1,2,4-thiadiazole **18**. Deketalization with 98% formic acid followed by reaction with amidinothiourea gave the desired **19**.



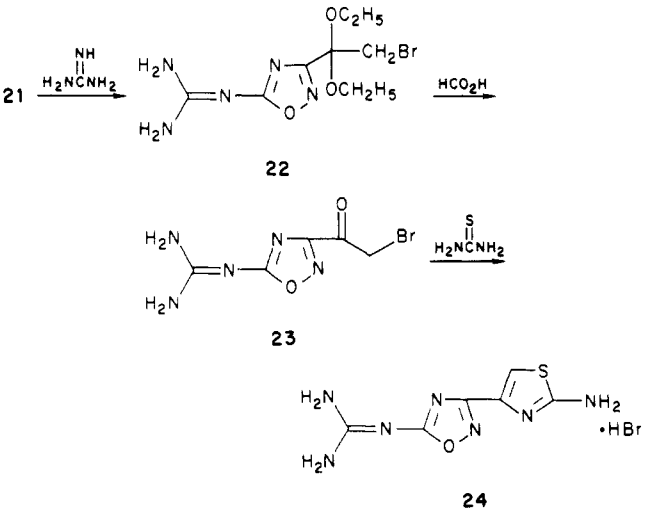
17 18 19

Thus far, the utility of NPBDP in the preparation of non-triazole derivatives of **1** has been described. NPBDP has also been used to prepare derivatives in which the 2-guanidinothiazole moiety has been replaced. Reaction of 3-bromo-2,2-diethoxypropionitrile (**16**) with hydroxylamine afforded a quantitative yield of amidoxime **20**. This could be converted to the 5-(trichloromethyl)-1,2,4-oxadiazole, **21**, by treatment with trichloroacetic anhydride.



20 21

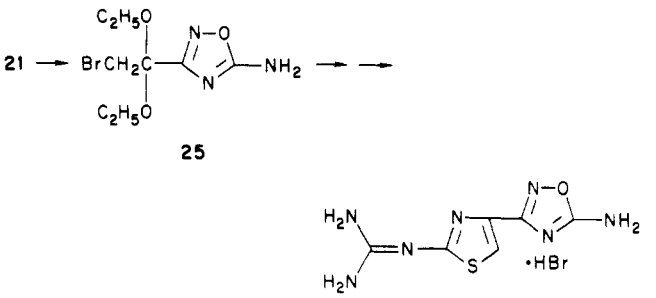
The trichloromethyl function is readily displaced by amines. Thus, reaction of **21** with guanidine afforded the 5-guanidino-1,2,4-oxadiazole, **22**. Deketalization to **23**, followed by reaction of this α-bromo ketone with thiourea, afforded **24**, an analogue of **1**, in which the 2-guanidinothiazole is replaced by a 5-guanidino-1,2,4-oxadiazole.



22 23 24

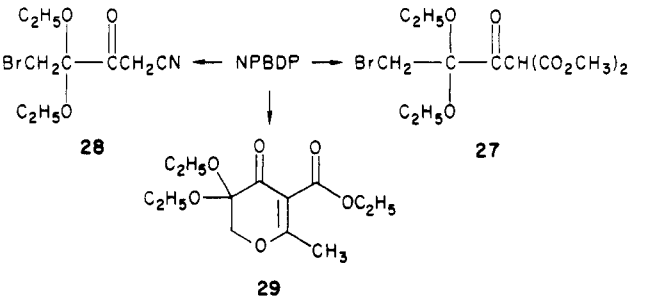
Similarly, treatment of **21** with ammonium acetate gave the 5-amino derivative **25**. Deketalization, followed by reaction with amidinothiourea, gave oxadiazole analogue **26**.

While the work described completed the primary goals of this work,[8] it was of interest to explore further the



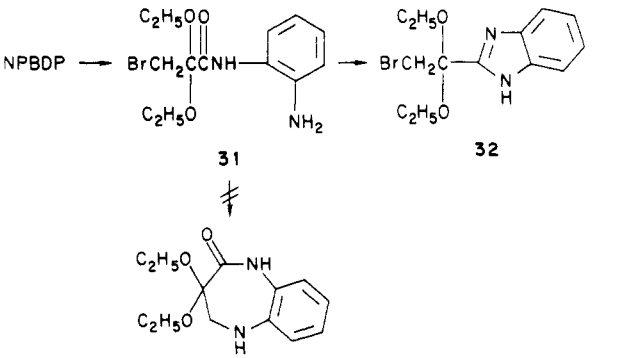
25 26

reactions of NPBDP in order to define its general utility. The chemoselective reactions of NPBDP with carbon nucleophiles such as sodium dimethyl malonate and lithium acetonitrile to give **27** and **28**, respectively, have been described.[1] However, while the α-bromoketal proved inert to intermolecular reaction, intramolecular reactions can occur when bifunctional nucleophiles are employed. Thus, treatment of NPBDP with the sodium salt of ethyl acetoacetate afforded only the 2,3-dihydro-γ-pyrone **29**, which results from initial adduct formation at the active ester, followed by cyclization via the enol form of this intermediate.



28 27 29

An attempt was made to take advantage of this mode of intramolecular cyclization in a benzodiazepine synthesis. Reaction of NPBDP with *o*-phenylenediamine did occur to give the amide adduct **31**. Surprisingly vigorous conditions were required for this transformation, which attests to the relatively low nucleophilicity of *o*-phenylenediamine as compared to the other nucleophiles used in this work. A variety of methods were explored in order to effect cyclization to the benzodiazepine. However, these resulted either in no reaction or cyclization to the benzimidazole **32**. Thus, it appears that while intramolecular cyclization of NPBDP adducts is possible, closure on the carbonyl to afford five-membered rings (**11** to **12** and **31** to **32**) is preferred to seven-membered ring formation.



31 32

In summary, NPBDP should prove to be a valuable reagent. It is a readily available, crystalline material, which

(8) A discussion of the biological activity of these compounds will appear elsewhere.

is of use as a building block for the preparation of a diverse array of organic molecules, such as highly functionalized small molecules, intermediates for natural product syntheses and heterocycles. The versatility of NPBDP should prove attractive in organic synthesis.

Experimental Section

^{1}H NMR spectra were obtained on a Varian T-60 spectrometer. Chemical shifts from tetramethylsilane are reported on the δ scale. Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Melting points are uncorrected and were obtained in open capillaries on a Thomas-Hoover melting point apparatus. Solvents and reagents were commercially available, unless otherwise noted, and were used directly.

Ethyl 2,2-Diethoxypropionate (4). A mixture of 34.8 g (0.30 mol) of ethyl pyruvate, 120 mL (0.72 mol) of triethylorthoformate, and 3 mL of concentrated sulfuric acid was stirred at room temperature for 3 h. The mixture was diluted with 300 mL of methylene chloride, then washed with water (2 × 100 mL), and saturated sodium chloride solution (1 × 100 mL). The organic solution was dried (Na_2SO_4), filtered, and evaporated, leaving a liquid. Distillation of this material afforded 56 g (98%) of **4** as a colorless liquid: bp 98 °C (20 torr) (lit.[4] bp 93–94 °C at (26 torr)); NMR ($CDCl_3$) δ 4.22 (q, 2 H), 3.53 (q, 4 H), 1.50 (s, 3 H), 1.4–1.0 (m, 9 H).

2,2-Diethoxypropionamide (5). A mixture of 35 g (0.18 mol) of **4** and 125 mL of ammonium hydroxide was placed in a steel bomb and heated at 150 °C for 4 h. The bomb was cooled, and the contents were removed and then concentrated. The residue was boiled with ether (2 × 100 mL), and the combined ether extracts were concentrated, leaving 10.5 g (36%) of **5** as a white solid: mp 60–63 °C; NMR ($CDCl_3$) δ 6.60 (b, 1 H), 6.10 (b, 1 H), 3.47 (q, 4 H), 1.50 (s, 3 H), 1.20 (t, 6 H). An analytical sample was prepared by sublimation, mp 65–66 °C. Anal. Calcd for $C_7H_{15}NO_3$: C, 52.14; H, 9.38; N, 8.69. Found: C, 51.69; H, 9.03; N, 8.89.

***N,N*-Dimethyl-*N'*-(2,2-diethoxy-1-propionyl)acetamidine (6).** A mixture of 10.0 g (62 mmol) of **5** and 40 mL (270 mmol) of *N,N*-dimethylacetamide dimethyl acetal was heated at reflux for 2 h. The mixture was concentrated and the residue distilled under reduced pressure to give 12.7 g (89%) of **6** as an amber oil; bp 122 °C (0.2 torr); NMR ($CDCl_3$) δ 3.57 (q, 4 H), 3.08 (s, 6 H), 2.25 (s, 3 H), 1.53 (s, 3 H), 1.23 (t, 6 H). This was used without further purification.

1-(3-Methyl-1,2,4-oxadiazol-5-yl)-1,1-diethoxyethane (7). Hydroxylamine hydrochloride (3.8 g, 54 mmol) was dissolved in 120 mL of 70% aqueous acetic acid, and 2.2 g (54 mmol) of sodium hydroxide was added. Once homogeneous, a solution of 10.5 g (45 mmol) of **6** in 60 mL of dioxane was added, and the mixture was heated at 100 °C (external) for 0.5 h. The mixture was cooled and then concentrated, and the residue was made basic with saturated $NaHCO_3$ solution. The aqueous solution was extracted with methylene chloride (3 × 30 mL), and the combined extracts were dried (Na_2SO_4), filtered, and evaporated, leaving 5.2 g of an oil. Distillation under reduced pressure afforded 4.6 g (50%) of **7** as a colorless liquid: bp 59 °C (0.2 torr); NMR ($CDCl_3$) δ 3.8–3.2 (m, 4 H), 2.43 (s, 3 H), 1.77 (s, 3 H), 1.27 (t, 6 H). Anal. Calcd for $C_9H_{16}N_2O_3$: C, 53.98; H, 8.05; N, 13.99. Found: C, 53.81; H, 8.09; N, 13.72.

1-(3-Methyl-1,2,4-oxadiazol-5-yl)ethanone (8). A mixture of 7.3 g (36 mmol) of **7**, 7.6 g (40 mmol) of *p*-TsOH, and 80 mL of acetone was heated at reflux for 2 h. The mixture was concentrated, and the residue was triturated with 50 mL of 20% Na_2CO_3 solution. The aqueous mixture was extracted with methylene chloride (3 × 20 mL), and the combined extracts were dried (Na_2SO_4), filtered, and evaporated, leaving a crude oil. Distillation under reduced pressure afforded 2.0 g (44%) of **8** as a colorless liquid, bp 108 °C (20 torr); NMR ($CDCl_3$) δ 2.73 (s, 3 H), 2.54 (s, 3 H). A sample of **8** was converted to its oxime for analytical purposes (oxime mp 162–164 °C). Anal. Calcd for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.77. Found: C, 42.38; H, 4.99; N, 29.68.

3-Bromo-2,2-diethoxypropionamide (10). A solution of 100 g (0.276 mol) of NPBDP (**3**)[1] in 750 mL of tetrahydrofuran was stirred at room temperature, and ammonia was slowly bubbled into the mixture over 2.5 h. The mixture was concentrated, and the residue was taken up into 600 mL of ethyl acetate and washed with 10% NaOH solution (4 × 150 mL). The ethyl acetate solution was dried (Na_2SO_4), filtered, and evaporated, leaving 62 g (94%) of **10** as a white solid: mp 144–146 °C; NMR ($CDCl_3$) δ 6.77 (b, 1 H), 6.35 (b, 1 H), 3.55 (s + q, 6 H), 1.25 (t, 6 H). An analytical sample (mp 146–147 °C) was prepared by recrystallization from cyclohexane. Anal. Calcd for $C_7H_{17}BrNO_3$: C, 35.02; H, 5.88; Br, 33.28; N, 5.83. Found: C, 35.30; H, 5.82; Br, 33.59; N, 5.96.

***O*-(3-Bromo-2,2-diethoxypropionyl)acetamide Oxime (11).** A mixture of 12.7 g (35 mmol) of NPBDP (**3**),[1] 2.6 g (35 mmol) of acetamide oxime,[9] and 200 mL of tetrahydrofuran was heated at reflux for 1 h. The mixture was concentrated, and the residue was taken up into 100 mL of chloroform. The chloroform solution was washed with 5% NaOH (4 × 30 mL), then dried (Na_2SO_4), filtered, and evaporated, leaving a white solid. Recrystallization from isopropyl ether afforded 6.7 g (64%) of **11** as a white crystalline solid: mp 119–120 °C; NMR ($CDCl_3$) δ 5.0 (b, 2 H), 3.56 (s + q, 6 H), 1.97 (s, 3 H), 1.19 (t, 6 H). Anal. Calcd for $C_9H_7BrN_2O_4$: C, 36.38; H, 5.77; N, 9.43; Br, 26.89. Found: C, 36.65; H, 5.70; N, 9.43; Br, 26.58.

5-(2-Bromo-1,1-diethoxyethyl)-3-methyl-1,2,4-oxadiazole (12). A mixture of 6.7 g (22.5 mmol) of *O*-(3-bromo-2,2-diethoxypropionyl)acetamide oxime (**11**), 100 mg of *p*-toluenesulfonic acid, and 100 mL of toluene was heated at reflux for 3 h. The mixture was concentrated, and the oil residue was distilled under reduced pressure to afford 4.1 g (66%) of **12** as a colorless oil: bp 106 °C (0.2 torr); NMR ($CDCl_3$) δ 3.77 (s, 2 H), 3.7–3.1 (m, 4 H), 2.39 (s, 3 H), 1.20 (t, 6 H). This was used without further purification. Anal. Calcd for $C_9H_{15}BrN_2O_3$: C, 38.73; H, 5.42; N, 10.04; Br, 28.63. Found: C, 38.51; H, 5.33; N, 9.98; Br, 28.75.

4-(3-Methyl-1,2,4-oxadiazol-5-yl)-2-guanidinothiazole Hydrobromide (14). A solution of 1.28 g (4.5 mmol) of **12** in 25 mL of 98% formic acid was heated at 85 °C (external) for 1 h. The mixture was cooled and then concentrated, leaving 5-(α-bromoacetyl)-3-methyl-1,2,4-oxadiazole (**13**): NMR ($CDCl_3$) δ 4.52 (s, 2 H), 2.48 (s, 3 H). This was dissolved in 25 mL of acetone, 0.53 g (4.5 mmol) of amidinothiourea[10] was added, and the mixture was heated at reflux for 3 h, during which time a white solid precipitated. This was collected by filtration, washed with ether, and dried in vacuo to give 0.55 g (41%) of **14** as a white solid; mp 250–251 °C; NMR (Me_2SO-d_6) δ 8.38 (s, 1 H), 8.30 (b, 4 H), 2.43 (s, 3 H). Anal. Calcd for $C_7H_8N_6OS$·HBr: C, 27.55; H, 2.97; N, 27.54; S, 10.51; Br, 26.19. Found: C, 27.12; H, 3.14; N, 27.23; S, 9.92; Br, 26.66.

3-Bromo-2,2-diethoxypropionitrile (16). A mixture of 53.5 g (0.223 mol) of 3-bromo-2,2-diethoxypropionamide (**10**), 500 mL of *p*-dioxane, and 36 mL (0.45 mol) of pyridine was stirred at room temperature under nitrogen, and 36 mL (0.25 mol) of trifluoroacetic anhydride was added via syringe over 2 min. The mixture was heated at reflux for 2 h and then stirred at room temperature for 1 h. The mixture was concentrated, and the residue was taken up into 300 mL of chloroform. The organic solution was washed with 100 mL of water and then with 100 mL of saturated sodium chloride solution. The organic solution was dried (Na_2SO_4), filtered, and evaporated, leaving an oil. Distillation under reduced pressure afforded 35.4 g (72%) of **16** as a pale yellow liquid: bp 76 °C (1.2 torr); NMR ($CDCl_3$) δ 3.76 (q, 4 H), 3.60 (s, 2 H), 1.30 (t, 6 H). Anal. Calcd for $C_7H_{12}BrNO_2$: C, 37.86; H, 5.45; N, 6.31. Found: C, 37.41; H, 5.07; N, 6.23.

3-Bromo-2,2-diethoxythiopropionamide (15). A solution of 5.6 g (25 mmol) of **16**, 15 g (60 mmol) of (diphenylphosphino)-dithoic acid,[11] and 120 mL of absolute ethanol was heated at 50 °C for 17 h. The mixture was concentrated, and the residue was taken up into 150 mL of ether. The ether solution was washed successively with 50-mL portions of water, 0.5 N sodium hydroxide solution, and saturated sodium bicarbonate solution, then dried (Na_2SO_4), filtered, and evaporated, leaving a crude solid. Re-

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crystallization from cyclohexane afforded 3.4 g (53%) of **15** as a white crystalline solid: mp 129 °C dec; NMR ($CDCl_3$) δ 7.85 (b, 1 H), 7.40 (b, 1 H), 3.82 (s, 2 H), 3.55 (q, 4 H), 1.23 (t, 6 H). Anal. Calcd for $C_7H_{14}BrNO_2S$: C, 32.82; H, 5.51; N, 5.47. Found: C, 32.68; H, 5.33; N, 5.44.

***N*,*N*-Dimethyl-*N'*-(3-bromo-2,2-diethoxy-1-thiopropionyl)amidine (17).** Dimethylformamide diethyl acetal (15 mL) was stirred at 5 °C, and 1.16 g (4.5 mmol) of **15** was added over 5 min. After addition was complete, the mixture was stirred at 5 °C for 1.5 h. The orange precipitate was collected by filtration, washed with a small amount of isopropyl ether, and dried in vacuo to give 1.05 g (75%) of **17** as an orange crystalline solid: mp 95–97 °C; NMR ($CDCl_3$) δ 8.43 (s, 1 H), 3.90 (s, 2 H), 3.64 (q, 4 H), 3.37 (s, 6 H), 1.27 (t, 6 H). An analytical sample, mp 101–102 °C, could be prepared by recrystallization from isopropyl ether. Anal. Calcd for $C_{10}H_{19}BrN_2O_2S$: C, 38.59; H, 6.15; N, 9.00; S, 10.30. Found: C, 38.77; H, 6.03; N, 8.48; S, 10.46.

5-(2-Bromo-1,1-diethoxyethyl)-1,2,4-thiadiazole (18). A solution of 1.05 g (3.3 mmol) of **17**, 0.55 mL (6.7 mmol) of pyridine, and 10 mL of absolute ethanol was stirred at room temperature, and a solution of 0.41 g (3.6 mmol) of hydroxylamine *O*-sulfonic acid in 5 mL of methanol was added directly. The heterogeneous mixture became homogeneous on addition. After being stirred at room temperature for 0.5 h, the mixture was concentrated (≤40 °C), and the residue was dissolved in 50 mL of methylene chloride. The organic solution was washed successively with 20-mL portions of water, 0.1 N sodium hydroxide solution, and water again, then dried (Na_2SO_4), filtered, and evaporated, leaving 0.71 g (77%) of **18** as a liquid: NMR ($CDCl_3$) δ 8.33 (s, 1 H), 3.90 (s, 2 H), 3.56 (m, 4 H), 1.27 (t, 6 H). This material was used without further purification.

4-(1,2,4-Thiadiazol-5-yl)-2-guanidinothiazole Hydrobromide (19). A solution of 1.0 g (3.6 mmol) of **18** and 20 mL of formic acid was heated at 85 °C for 1 h. The solution was concentrated, triturated with 25 mL of ether, and filtered to remove insolubles. Concentration of the ether solution left an oil that was dissolved in 25 mL of acetone. Amidinothiourea[10] (0.35 g, 3.0 mmol) was added, and the mixture was heated at reflux for 1 h. The mixture was cooled to room temperature, and the precipitate was collected by filtration, washed well with acetone, and dried in vacuo to give 0.27 g (32%) of pure **19** as a white solid: mp > 275 °C; NMR (Me_2SO-d_6) δ 8.70 (s, 1 H), 8.05 (b + s, 5 H). Anal. Calcd for $C_6H_6N_6S_2$·HBr: C, 23.46; H, 2.30; N, 27.36; S, 20.88; Br, 26.00. Found: C, 23.86; H, 2.62; N, 26.71; S, 20.74; Br, 25.54.

3-Bromo-2,2-diethoxypropionamidoxime (20). A solution of 3.6 g (54 mmol) of 85% potassium hydroxide in 70 mL of methanol was stirred at room temperature, and to this was added a warm solution of 3.7 g (54 mmol) of hydroxylamine hydrochloride in 70 mL of methanol. Potassium chloride precipitated, and this was removed by filtration. To the filtrate was added 10.0 g (45 mmol) of 3-bromo-2,2-diethoxypropionitrile (**16**), and the solution was heated at 50 °C for 3.5 h. The mixture was concentrated, leaving a solid. This was triturated with hexane, then filtered, and dried in vacuo to afford 11.6 g (100%) of **20** as a white solid, mp 132–135 °C. An analytical sample, mp 137.5–139 °C, can be prepared by recrystallization from ethanol. Anal. Calcd for $C_7H_{15}BrN_2O_3$: C, 32.95; H, 5.93; N, 10.98. Found: C, 32.55; H, 5.65; N, 10.83.

3-(2-Bromo-1,1-diethoxyethyl)-5-(trichloromethyl)-1,2,4-oxadiazole (21). To a mixture of 7.2 g (28 mmol) of 3-bromo-2,2-diethoxypropionamidoxime (**20**) and 18.3 g (112 mmol) of trichloroacetic acid was added 10.2 mL (56 mmol) of trichloroacetic anhydride. This mixture was immediately heated at 60 °C (external) with rapid stirring for 5 min. The mixture was cooled to 0 °C and then diluted with 420 mL of chloroform. The organic solution was washed with saturated sodium bicarbonate solution (3 × 45 mL), dried (Na_2SO_4), filtered, and evaporated, leaving a white solid. This was triturated with 75 mL of hexane, and the insoluble solid was removed by filtration. This amounted to 5.4 g (75% recovery) of unreacted 3-bromo-2,2-diethoxypropionamidoxime (**20**). Concentration of the hexane filtrate afforded 2.1 g (20%) of the product **21** as a white solid: mp 74.5–76.5 °C; NMR ($CDCl_3$) δ 3.87 (s, 2 H), 3.63 (m, 4 H), 1.30 (t, 6 H). Attempts to get complete conversion of **20** to **21** resulted in decomposition of **21**. This procedure, albeit inefficient, proved the simplest. Anal. Calcd for $C_9H_{12}BrCl_3N_2O_3$: C, 28.26; H, 3.16; N, 7.32. Found: C, 28.48; H, 3.21; N, 7.30.

3-(2-Bromo-1,1-diethoxyethyl)-5-guanidino-1,2,4-oxadiazole (22). Sodium (0.27 g, 12 mmol) was dissolved in 45 mL of absolute ethanol at room temperature under a nitrogen atmosphere, and to this was added 0.96 g (10 mmol) of guanidine hydrochloride. Sodium chloride, which precipitated, was removed by filtration, and to the filtrate was added 2.69 g (7.0 mmol) of **21**. A precipitate immediately formed. The mixture was stirred at room temperature for 15 min, and the precipitate was collected and dried in vacuo to give 1.65 g (73%) of **22** as a white solid: mp 239–240 °C; NMR (Me_2SO-d_6) δ 8.12 (b, 4 H), 3.78 (s, 2 H), 3.36 (m, 4 H), 1.08 (t, 6 H). Anal. Calcd for $C_9H_{16}BrN_5O_3$: C, 33.55; H, 5.01; H, 21.74. Found: C, 33.51; H, 4.99; N, 21.56.

3-(2-Amino-4-thiazolyl)-5-guanidino-1,2,4-oxadiazole Hydrobromide (24). A mixture of 530 mg (1.60 mmol) of **22** in 8 mL of 98% formic acid was heated at 85 °C for 1 h. The mixture was concentrated, leaving 409 mg of 2-bromo-(5-guanidino-1,2,4-oxadiazol-5-yl)-1-ethanone (**23**) as a white solid. This was dissolved in 10 mL of acetone, 128 mg (1.60 mmol) of thiourea[10] was added, and the mixture was heated at reflux for 2 h. The precipitate was collected by filtration, washed with methanol, and dried in vacuo to give 276 mg (56%) of **24** as a white solid, mp 250–252 °C dec. Anal. Calcd for $C_6H_7N_7OS$·HBr: C, 23.54; H, 2.63; N, 32.03. Found: C, 23.43; H, 2.76; N, 31.36.

5-Amino-3-(2-bromo-1,1-diethoxyethyl)-1,2,4-oxadiazole (25). A mixture of 500 mg (1.30 mmol) of **21**, 277 mg (3.9 mmol) of ammonium acetate, and 10 mL of absolute ethanol was heated at reflux for 1 h. The mixture was concentrated, and the residue was first triturated with hexane (to remove any unreacted **21**), decanted, and then triturated with water (to remove the excess ammonium acetate). The resulting solid was washed with water and then dried in vacuo to give 272 mg (75%) of **25** as a white solid: mp 160–162.5 °C; NMR (Me_2SO-d_6) δ 7.67 (b, 2 H), 3.77 (s, 2 H), 3.5 (m, 4 H), 1.19 (t, 6 H). Anal. Calcd for $C_8H_{14}BrN_3O_3$: C, 34.30; H, 5.04; N, 15.00. Found: C, 34.17; H, 4.98; N, 14.90.

4-(5-Amino-1,2,4-oxadiazol-3-yl)-2-guanidinothiazole Hydrobromide (26). A mixture of 173 mg (0.62 mmol) of **25** and 3 mL of 98% formic acid was heated at 85 °C for 1 h. The mixture was concentrated, leaving 109 mg of a white solid. This was dissolved in 6 mL of acetone, 70 mg (0.6 mmol) of amidinothiourea[10] was added, and the mixture was heated at reflux for 1 h. The resulting precipitate was collected by filtration, washed with acetone, and dried in vacuo to give 115 mg (71%) of **26** as a white solid: mp >300 °C; NMR (Me_2SO-d_6) δ 8.25 (b, 4 H), 7.90 (b, 2 H), 7.78 (s, 1 H). Anal. Calcd for $C_6H_7N_7OS$·HBr: C, 23.54; H, 2.63; N, 32.03. Found: C, 23.57; H, 2.82; N, 31.55.

Methyl 5-Bromo-2-carbomethoxy-4,4-diethoxy-3-oxopentanoate (27). A slurry of 1.06 g (44 mmol) of sodium hydride in 75 mL of dry tetrahydrofuran was stirred at room temperature under nitrogen, and 5.55 g (42 mmol) of dimethyl malonate was added dropwise over 10 min. After addition was complete, the solution was stirred at room temperature for 20 min and then a solution of 7.24 g (20 mmol) of NPBDP (**3**)[1] in 50 mL of dry tetrahydrofuran was added dropwise over 5 min. After addition was complete, the mixture was stirred at reflux for 2 h. The mixture was cooled and poured into 400 mL of ice water, and the aqueous mixture was brought to pH 6 with dilute hydrobromic acid. The aqueous mixture was extracted (3 × 70 mL) with chloroform. The combined extracts were dried (Na_2SO_4), filtered, and evaporated, leaving an oil. This was chromatographed over 200 g of silica gel using 4:1 hexane/ethyl acetate as eluent to give 4.4 g of the product as a colorless oil. Trituration of this oil with low boiling petroleum ether resulted in crystallization of the oil. Recrystallization of this material from hexane afforded 3.9 g (55%) of **27** as a white crystalline solid: mp 81–83 °C; NMR ($CDCl_3$) δ 5.17 (s, 1 H), 3.80 (s, 6 H), 3.63 (q, 4 H), 3.50 (s, 2 H), 1.23 (t, 6 H). Anal. Calcd for $C_{12}H_{19}BrO_7$: C, 40.58; H, 5.39. Found: C, 40.44; H, 5.28.

5-Bromo-4,4-diethoxy-3-oxovaleronitrile (28). Tetrahydrofuran (85 mL dried over molecular sieves) was placed in a three-necked, 500-mL, round-bottom flask, fitted with an overhead stirrer, addition funnel, and thermometer. The flask was cooled to −70 °C under a nitrogen atmosphere, and 57 mL (90 mmol) of a 1.6 M solution of *n*-butyllithium in hexane (Foote Chemical Co.) was added over 20 min. To this mixture was added a solution

of 3.7 g (90 mmol) of acetonitrile in 85 mL of THF over 45 min. After addition was complete, the mixture was stirred at −70 °C for 1 h, and then a solution of 16.3 g (45 mmol) of NPBDP (3)[1] in 85 mL of THF was added dropwise over 30 min. After the addition was complete, the mixture was stirred at −70 °C for 30 min and then allowed to warm to room temperature. The mixture was quenched with 125 mL of 1 N hydrobromic acid solution. The organic layer was separated, and the aqueous portion was washed with ether (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated, leaving an oil which consisted of *p*-nitrophenol and the product by TLC. The oil was chromatographed over 400 g of silica gel using chloroform/cyclohexane (5:1) as eluent. The product, which was less polar than *p*-nitrophenol, eluted in fractions 35–105 (12-mL portions) and amounted to 10.9 g (92%) of a white solid: mp 66–68 °C; NMR ($CDCl_3$) δ 3.83 (s, 2 H), 3.7–3.2 (m, 6 H), 1.14 (t, 6 H). Anal. Calcd for $C_9H_{14}BrNO_3$: C, 40.93; H, 5.34; N, 5.30. Found: C, 40.95; H, 5.21; N, 5.40.

Ethyl 2,3-Dihydro-3,3-diethoxy-6-methyl-4-pyrone-5-carboxylate (29). A slurry of 1.06 g (22 mmol) of 50% sodium hydride in 50 mL of tetrahydrofuran (dried over molecular sieves) was stirred at room temperature under a nitrogen atmosphere, and to this was added, dropwise over 15 min, a solution of 2.73 g (21 mmol) of ethyl acetoacetate in 10 mL of tetrahydrofuran. After addition was complete, the mixture was stirred at room temperature for 15 min and then a solution of 3.62 g (10 mmol) of NPBDP (3)[1] in 40 mL of tetrahydrofuran was added dropwise over 5 min. The mixture was heated at reflux for 4 h, and the heterogeneous mixture was cooled and then poured into 200 mL of ice water. The pH of the solution was brought to 7 with dilute hydrobromic acid solution, and the mixture was extracted with chloroform (4 × 30 mL). The combined extracts were dried (Na_2SO_4), filtered and evaporated, leaving an oil which consisted of *p*-nitrophenol and product. Separation was effected by chromatography over silica gel (120 g) using isopropyl ether as eluent. *p*-Nitrophenol eluted first. The second material amounted to 1.58 g (58%) of **29** as a colorless oil; bp 126 °C (0.8 torr); NMR ($CDCl_3$) δ 4.33 (s, 2 H), 4.25 (q, 2 H), 3.65 (q, 4 H), 2.23 (s, 3 H), 1.4–1.0 (m, 9 H). Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34, H, 7.40. Found: C, 57.12; H, 7.28.

4-Ethoxy-3-(cyanomethyl)pyrazole (30). A mixture of 2.64 g (10 mmol) of 5-bromo-4,4-diethoxy-3-oxovaleronitrile (**28**), 0.51 mL of 99% hydrazine hydrate, and 40 mL of absolute ethanol was heated at reflux for 1 h. Another equivalent of hydrazine hydrate was added at this point, and refluxing was continued for another hour. The mixture was cooled, insolubles were removed by filtration, and the filtrate was concentrated, leaving a viscous oil. This was chromatographed over 70 g of silica gel using 2:1 ethyl acetate/hexane as eluent. The product amounted to 845 mg (56%) of an off-white solid: mp 78–81 °C; NMR (Me_2SO-d_6) δ 7.45 (s, 1 H), 3.90 (q, 2 H), 3.80 (s, 2 H), 1.25 (t, 3 H); IR (KBr) 2449 cm^{-1} (CN). An analytical sample was prepared by recrystallization from 1:1 ethyl acetate/hexane, mp 80–82 °C. Anal. Calcd for $C_7H_9N_3O$: C, 55.62; H, 6.00; N, 27.80. Found: C, 56.00; H, 5.99; N, 27.64.

***N*-(2-Anilino)-3-bromo-2,2-diethoxypropionamide (31).** A mixture of 7.2 g (20 mmol) of NPBDP (3),[1] 2.4 g (22 mmol) of *o*-phenylenediamine, and 60 mL of dimethylformamide was heated at 150 °C (external) for 3 h. At this point, another 0.5 g (4.6 mmol) of *o*-phenylenediamine was added to the mixture, and heating was continued for another 1.5 h. The mixture was cooled and then concentrated. The residue was dissolved in 75 mL of ethyl acetate, and the organic solution was washed with 5% sodium hydroxide solution (3 × 25 mL). The organic solution was dried (Na_2SO_4), filtered, and evaporated, leaving 6 g of a crude solid. This was purified by chromatography over 130 g of silica gel using 19:1 isopropyl ether/ethyl acetate as eluent to give an off-white solid. Recrystallization from cyclohexane afforded 3.64 g (55%) of **31** as a white crystalline solid: mp 91–92 °C; NMR ($CDCl_3$) δ 8.40 (b, 1 H), 7.3–6.6 (m, 4 H), 4.0–3.4 (m, 8 H), 1.32 (t, 6 H). Anal. Calcd for $C_{13}H_{19}BrN_2O_3$: C, 47.15; H, 5.78; N, 8.46. Found: C, 47.63; H, 5.78; N, 8.07.

2-(2-Bromo-1,1-diethoxy-1-ethyl)benzimidazole (32). A mixture of 3.2 g (9.7 mmol) of *N*-(2-anilino)-3-bromo-2,2-diethoxypropionamide (**31**) and 50 mL of 97% formic acid was warmed to 80 °C and heated at this temperature for 2.5 h. The dark solution was concentrated, and the solid residue was triturated with saturated $NaHCO_3$ and then extracted into ether (4 × 50 mL). The ether extracts were dried (Na_2SO_4), filtered, and evaporated, leaving an oil. Chromatography over 75 g of silica gel using 9:1 ether/ethyl acetate as eluent afforded 2.36 g (78%) of **32** as a tan solid: mp 124–127 °C; NMR ($CDCl_3$) δ 7.6–7.0 (m, 4 H), 3.69 (s, 2 H), 3.61 (q, 4 H), 1.26 (t, 6 H). Anal. Calcd for $C_{13}H_{17}BrN_2O_2$: C, 49.85; H, 5.47; N, 8.94. Found: C, 49.38; H, 5.10; N, 8.51.

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Registry No. **3**, 87224-03-1; **4**, 7476-20-2; **5**, 92845-55-1; **6**, 92845-56-2; **7**, 92845-57-3; **8**, 92845-58-4; **8** (oxime), 92845-71-1; **10**, 87224-04-2; **11**, 87224-05-3; **12**, 87224-09-7; **13**, 87224-10-0; **14**, 92900-60-2; **15**, 87224-11-1; **16**, 87246-24-0; **17**, 92845-59-5; **18**, 92845-60-8; **18** (ketone), 92845-72-2; **19**, 92845-61-9; **20**, 92845-62-0; **21**, 92845-63-1; **22**, 92845-64-2; **23**, 92845-65-3; **24**, 92845-66-4; **25**, 92845-67-5; **25** (ketone), 92845-73-3; **26**, 92845-68-6; **27**, 87246-23-9; **28**, 87224-07-5; **29**, 87224-06-4; **30**, 87224-08-6; **31**, 92845-69-7; **32**, 92845-70-0; $CH_3COCO_2C_2H_5$, 617-35-6; $CH(OC_2H_5)_3$, 122-51-0; $CH_3C(OCH_3)_2N(CH_3)_2$, 18871-66-4; $NH_2OH{\cdot}HCl$, 5470-11-1; $CH_3C(NH_2)=NOH$, 22059-22-9; $H_2NCSN=C(NH_2)_2$, 2114-02-5; Ph_2PS_2H, 1015-38-9; $HC(OC_2H_5)_2N(CH_3)_2$, 1188-33-6; H_2NOSO_3H, 2950-43-8; Cl_3CCO_2H, 76-03-9; $H_2NC(NH_2)=NH{\cdot}HCl$, 50-01-1; H_2NCSNH_2, 62-56-6; $NH_4^+CH_3CO_2^-$, 631-61-8; $CH_2(CO_2CH_3)_2$, 108-59-8; CH_3CN, 75-05-8; $CH_3COCH_2CO_2C_2H_5$, 141-97-9; N_2H_4, 302-01-2; *o*-$H_2NC_6H_4NH_2$, 95-54-5.

Functionalized 13-Crown-4, 14-Crown-4, 15-Crown-4, and 16-Crown-4 Compounds: Synthesis and Lithium Ion Complexation[1]

Bronislaw P. Czech, David A. Babb, Byungki Son, and Richard A. Bartsch*

Department of Chemistry, Texas Tech University, Lubbock, Texas 79409

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Seven novel (benzyloxy)methyl-substituted crown ethers with four ring oxygens and 13-, 14-, 15-, and 16-membered polyether rings are synthesized and their lithium and sodium cation-binding abilities are assessed by solvent extraction of the aqueous alkali metal picrates. Strongest lithium ion complexation is observed with [(benzyloxy)methyl]-14-crown-4 compounds.

The design and synthesis of selective lithium ion complexing agents has recently received considerable attention. Among the crown ethers, benzo-13-crown-4 and dibenzo-14-crown-4 were found to exhibit efficient and selective

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