Quaternary Salts of 2-[(Hydroxyimino)methyl]imidazole. 3. Synthesis and Evaluation of (Alkenyloxy)-, (Alkynyloxy)-, and (Aralkyloxy)methyl Quaternarized 2-[(Hydroxyimino)methyl]-1-alkylimidazolium Halides as Reactivators and Therapy for Soman Intoxication

Clifford D. Bedford,*,† Ralph N. Harris, III,*,‡ Robert A. Howd,‡ Dane A. Goff,‡ Gary A. Koolpe,‡ M. Petesch,‡ Irwin Koplovitz,§ Walter E. Sultan,§ and H. A. Musallam⊥

Organic Chemistry Department and Biomedical Research Laboratory, SRI International, Menlo Park, California 94025, Drug Testing and Evaluation Branch, U.S. Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Maryland 21010, and Department of Medicinal Chemistry, Walter Reed Army Institute of Research, Washington, D.C. 20307.
Received February 29, 1988

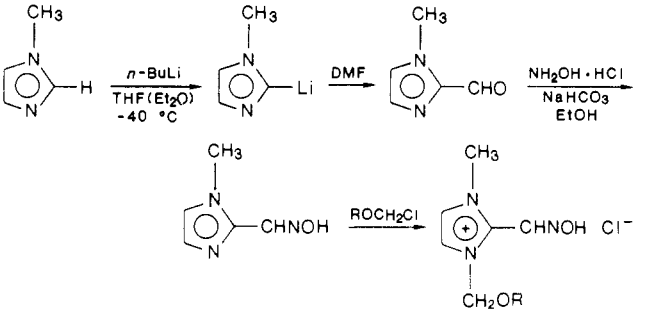
A series of structurally related monosubstituted 1-[(alkenyloxy)methyl]-, 1-[(alkynyloxy)methyl]-, and 1-[(aralkyloxy)methyl]-2-[(hydroxyimino)methyl]-3-methylimidazolium halides were prepared and evaluated. All new compounds were characterized with respect to (hydroxyimino)methyl acid dissociation constant, nucleophilicity, and octanol–buffer partition coefficient. The alkynyloxy-substituted compounds were also evaluated in vitro with respect to reversible inhibition of human erythrocyte (RBC) acetylcholinesterase (AChE) and kinetics of reactivation of human AChE inhibited by ethyl *p*-nitrophenyl methylphosphonate (EPMP). In vivo evaluation in mice revealed that coadministration of alkynyloxy-substituted imidazolium compounds with atropine sulfate provided significant protection against a 2 × LD_{50} challenge of GD. For the alkynyloxy-substituted imidazolium drugs there is a direct relationship between in vitro and in vivo activity: the most potent in vivo compounds against GD proved to be potent in vitro reactivators against EPMP-inhibited human AChE. These results differ from the observations made on the sterically hindered imidazolium compounds (see previous article) and suggest that several antidotal mechanisms of protective action may be applicable for the imidazolium aldoxime family of therapeutics. The ability of the alkynyloxy substituents to provide life-saving protection against GD intoxication was not transferable to the pyridinium or triazolium heteroaromatic ring systems.

Although the highly toxic nature of organophosphorus compounds has been known for many years,[1-10] there still exists serious limitations in the antidotal therapy available against poisoning of these compounds. Most toxic organophosphorus esters are irreversible inhibitors of acetylcholinesterase (acetylcholine hydrolase, AChE).[1,11-13] Conventional therapy against organophosphorus ester intoxication entails coadministration of atropine that antagonizes the effects of accumulated acetylcholine and an AChE "reactivator" that restores enzyme activity.[14-17]

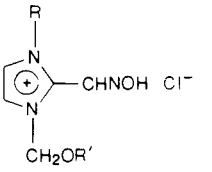
Currently, pyridinium aldoximes are the only clinically used reactivators. This conventional treatment is effective for general organophosphorus esters including the chemical warfare agents sarin (GB) and VX but is unsuccessful in cases of soman (GD) or tabun (GA) intoxication. The standard therapeutics are ineffective in animal studies in preventing or treating intoxication by 3,3-dimethyl-2-butyl methylphosphonofluoridate (GD) when GD is administered in quantities exceeding approximately 1.5 times the LD_{50} or GA when administered in quantities exceeding approximately 2.5 times the LD_{50}.

In the previous article,[18] a series of 2-[(hydroxyimino)-methyl]-3-methyl-1-(alkoxymethyl)-substituted imidazolium halides, 1, were examined for activity in vitro versus electric eel, bovine, and human AChE inhibited by ethyl *p*-nitrophenyl methylphosphonate (EPMP) and GD and in vivo in the mouse against an EPMP and GD challenge. These studies revealed a particularly high ability of the imidazolium oxime compounds toward reactivating phosphonated AChE with only moderate reversible inhibition of the enzyme.[18,19] These findings suggested that the imidazole ring system is an excellent backbone for structural "fine tuning" to improve maximal activity.

Scheme I



Accordingly, 55 new 3-methyl-1-unsaturated alkoxymethyl quaternary type 1 compounds and derivatives



1

† Organic Chemistry Department, SRI International. Present address: Naval Surface Warfare Center, Code R-11, White Oak Laboratories, Silver Spring, MD 20910.

‡ Organic Chemistry Department and Biomedical Research Laboratory, SRI International.

§ U.S. Army Medical Research Institute of Chemical Defense.

⊥ Walter Reed Army Institute of Research.

(1) Heath, D. F. *Organophosphorus Poisons-Anticholinesterases and Related Compounds*; Pergamon: New York, 1961.
(2) Spear, R. C.; Jenkins, D. L.; Milby, T. H. *Environ. Sci. Technol.* **1975**, *9*, 308.
(3) Milby, T. H. *JAMA, J. Am. Med. Assoc.* **1971**, *216*, 2131.
(4) Koller, W. C.; Klawans, H. L. *Handb. Clin. Neurol.* **1979**, 37, 541.
(5) Baker, E. L.; Warren, M.; Zack, M.; Dobbin, R. D.; Miles, J. W.; Miller, S.; Alderman, L.; Teeters, W. R. *Lancet* **1978**, *1*, 31.
(6) Koelle, G. B. In *The Pharmacological Basis of Therapeutics*; Goodman, L., Gilman, A., Eds.; MacMillan: New York, 1965; p 404.
(7) Sim, V. M. In *Drill's Pharmacology in Medicine*, 3rd ed; McGraw-Hill: New York, 1965; p 971.
(8) Harris, B. L.; Shanty, F. *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed.; Wiley: New York, 1980; Vol. 5, p 393.
(9) Meselson, M.; Robinson, J. *S. Am.* **1980**, *242*, 39.
(10) Stockholm International Peace Research Institute, *The Problems of Chemical and Biological Warfare*; Humanities Press: New York, 1973; Vol. 2, p 17.

0022-2623/89/1832-0504$01.50/0

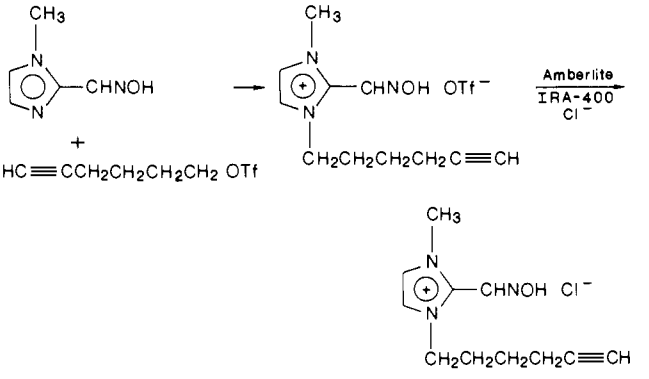
representing the 2-[(hydroxyimino)methyl]-3-methylimidazolium ring system were synthesized. As before, all compounds were evaluated with respect to (hydroxyimino)methyl acid dissociation constant, nucleophilicity, and lipophilicity. The alkynyloxy-substituted imidazolium derivatives were also evaluated for reversible inhibition of AChE and kinetics of reactivating EPMP-inhibited AChE. Additionally, the new imidazolium oximes were examined in vivo in mice against a GD challenge. Compounds that demonstrated excellent protective ability against GD were also screened against GA.

Results and Discussion

Synthesis, Structure, and Acidity. The 3-methyl-1-[(alkenyloxy)methyl]imidazolium halides, compounds **2**, 3-methyl-1-[(alkynyloxy)methyl]imidazolium halides, compounds **3**, and the 3-methyl-1-[(aralkyloxy)methyl]-imidazolium compounds **4** were prepared by the general synthesis route shown in Scheme I. As previously described,[19] 1-methylimidazole was converted to the corresponding 2-carboxaldehyde derivative by a modified version of the Iversen and Lund method.[20] The aldehydes were converted to the oxime derivative in standard fashion. Quaternization of the imidazole ring with selected chloromethyl ethers prepared from their respective alcohols[21-23] provided the desired quaternary salts **2**, **3**, and **4**. Table I provides structures and selected physicochemical data for new compounds.

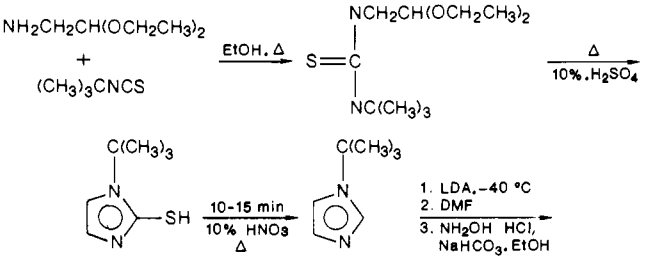
In addition to the 46 new unsaturated [(alkyloxy)-methyl]imidazolium compounds, a variety of hexynyl-substituted imidazolium compounds were prepared, compounds **5–8**. The hexynyl functional group was selected for further investigation based on the high degree of in vivo activity demonstrated against GD (vide infra). For compound **5**, 1-methylimidazole was treated with the 5-hexyn-1-ol triflate to yield the imidazolium triflate, which was converted to the chloride salt by ion exchange. The triflate alkylating agents were found to be the most effective alkylating agents. They were selected over alkyl halides, tosylates, or mesylates because of their enhanced reactivity toward heteroaromatic ring systems. For example, alkylation of the triazole ring system using alkyl iodides required up to 3 months at 50 °C to complete. With the triflate alkylating agents, the reaction was generally complete within an hour.

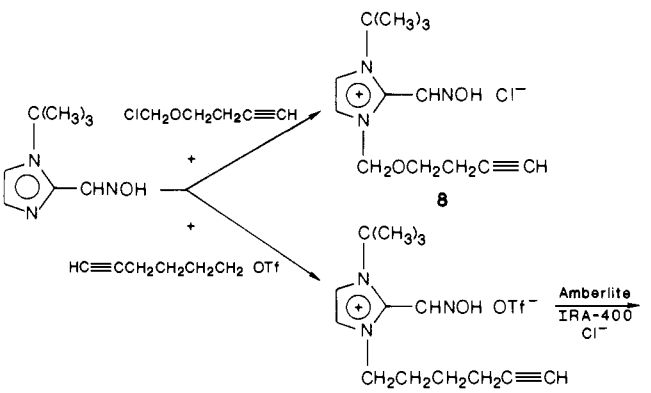
The two *tert*-butylimidazolium compounds, **6** and **8**, were prepared by treating 2-[(hydroxyimino)methyl]-1-*tert*-butylimidazole with the appropriate alkylating agent, 5-hexyn-1-ol triflate and 1-but-3-ynyl chloromethyl ether,



5

respectively, followed by ion exchange where needed.

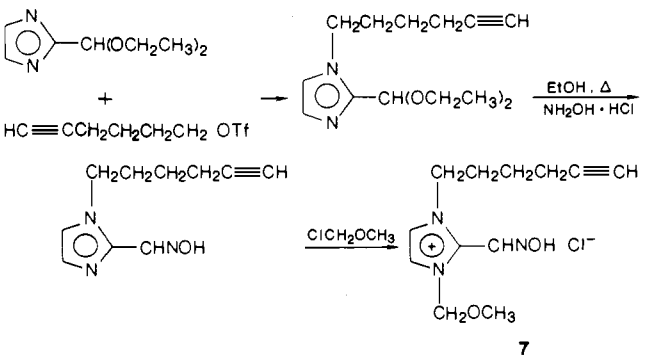




8

6

Compounds **7** and **9** were prepared in the typical manner by treating the appropriate imidazole precursor with either an alkynyl or allenic alkylating agent.

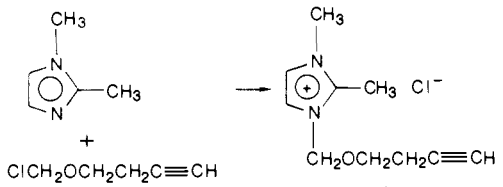


7

Compound **10** was synthesized to explore the possible interactions between AChE and the [(alkynyloxy)-methyl]-substituted imidazolium compound in the absence of a reactivator moiety. This compound was prepared by

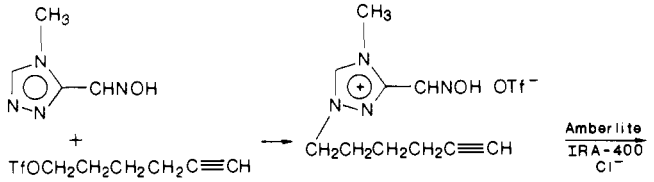
(11) Karczmar, A. G. *Int. Encycl. Pharmacol. Ther.* **1970**, *1*, 1.
(12) Usdin, E. *Int. Encycl. Pharmacol. Ther.* **1970**, *1*, 47.
(13) Englehard, N.; Prchal, K.; Nenner, M. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 615.
(14) Wills, J. H. *Int. Encycl. Pharmacol. Ther.* **1970**, *1*, 357.
(15) Namba, T.; Nolte, C. T.; Jackrel, J.; Grob, D. *Am. J. Med.* **1971**, *50*, 475.
(16) McNamara, B. D. *Oximes as Antidotes in Poisoning by Anticholinesterase Compounds*; Edgewood Arsenal Special Publication 5B-SP-76004, NTIS AD-AO123243, 1976.
(17) Ellin, R. I.; Wills, J. H. *J. Pharmaceut. Sci.* **1964**, *53*, 995.
(18) Bedford, C. D.; Harris, R. H.; Howd, R. A.; Goff, D.; Koolpe, G. A.; Broussard, M.; Miller, A.; Nolen, H. W.; Musallam, H. A.; Pick, R. O.; Jones, D. E.; Koplovitz, I.; Sultan, W. E. *J. Med. Chem.*, preceding article in this issue.
(19) Bedford, C. D.; Harris, R. N.; Howd, R. A.; Kenley, R. A.; Miller, A.; Noeln, H. W. *J. Med. Chem.* **1984**, *27*, 1431.
(20) Iversen, P. E.; Lund, H. *Acta Chem. Scand.* **1966**, *20*, 2549.
(21) Walker, J. F.; Chadwick, A. F. *Ind. Eng. Chem.* **1947**, *39*, 977.
(22) Hill, A. J.; Keach, D. T. *J. Am. Chem. Soc.* **1926**, *48*, 259.
(23) Harris, R. H.; Goff, D.; Bottaro, J.; Bedford, C. D. *J. Org. Chem.* **1986**, *51*, 4711.

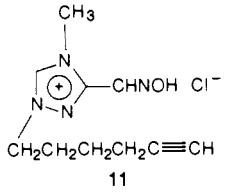
treating 1,2-dimethylimidazole with 1-but-3-ynyl chloromethyl ether.



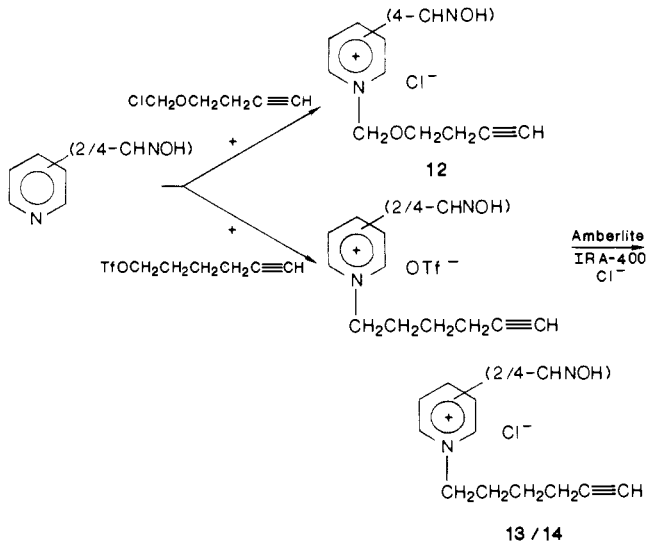
10

Finally, a series of non-imidazolium oximes was prepared. The substituents on these triazolium and pyridinium reactivators were selected on the basis of the remarkable activity shown by the [(alkynyloxy)methyl]-imidazolium compounds. Since reactivation potency against a GD challenge was based on the alkynyl or (alkynyloxy)methyl substituent, it was of interest to determine whether this efficacy would be independent of the quaternary ring system. Furthermore, changes in the heteroaromatic ring backbone may provide compounds with improved therapeutic values (i.e., compounds with reduced toxicity while maintaining high therapeutic activity). Compounds 11 through 14 were prepared by treating the appropriate ring system with an alkynyl or (alkynyloxy)-methyl alkylating agent followed by ion exchange over IRA-400 Amberlite chloride resin when necessary. Table





11



12

13 / 14

II provides structures and selected physicochemical data for new quaternary compounds **5–14**.

All the unsaturated alkoxymethyl-substituted mono-imidazolium oximes (compounds **2**, **3**, and **4**) exhibit an acid dissociation constant (pKa) near 8.0. In contrast, the triazolium oxime 11 exhibited a lower pK_a of 7.34. The lower pK_a of the oximate anion is attributed to increased charge delocalization through the ring heteroatoms and increased ring electronegativity. This increased electronegativity also accounts, in part, for the decreased solvolytic stability of the triazolium alkoxymethyl compounds. All attempts to prepare the alkoxymethyl-substituted triazolium oximes failed, yielding instead, the hydrochloride salts resulting from decomposition of the initially quaternarized material. The lower pK_a for these derivatives leads to an increase in effective oximate anion concentration at physiological pH, which should lead to more effective reactivation, since it is the oximate anion that serves as the attacking species on phosphorus.[24,25] However, the increase oximate anion concentration is offset somewhat by the reduced nucleophilicity of the oximate anion as previously noted.[26-29]

The oximes were obtained only as the *E* isomer as previously reported.[18,19] The quaternary salts were also all obtained configurationally pure as evidenced by proton NMR spectra. They all exhibited chemical shift values for the oxime hydroxyl proton between δ 12.50 and 13.50 ppm. By analogy with previous results, the *E* configuration has been assigned to the imidazolium aldoxime derivatives examined in this report.

For each compound tested in vitro, the observed thiocholine production rates (d[thiocholine]/d*t*) were invariant to within SD = ±10% over the 4- to 6-h incubation period normally used in our in vitro assay. This, coupled with UV spectra of the test compounds at pH 6.4, 7.6, and 8.5 taken over a 24-h period, excluded the possibility of significant hydrolytic degradation of the test compounds under the assay conditions used.[26-29]

Reversible Acetylcholinesterase Inhibition. In previous investigations[18,19,26-29] with EPMP-inhibited AChEs, it has been established that the interactions of the imidazolium aldoximes with EPMP-inhibited AChE and free enzyme are adequately described by eq 1–5:

$$EI + R \underset{}{\overset{K_r}{\rightleftharpoons}} [EI\cdot R] \quad (1)$$

$$[EI\cdot R] \xrightarrow{k_r} E \quad (2)$$

$$E + R \underset{}{\overset{K_i}{\rightleftharpoons}} [E\cdot R] \quad (3)$$

$$EI \xrightarrow{k_{sp}} E \quad (4)$$

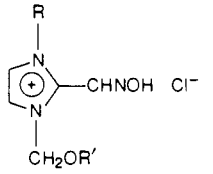
$$HOX \underset{}{\overset{K_a}{\rightleftharpoons}} OX^- + H^+ \quad (5)$$

where R is a test compound, EI is EPMP-inhibited AChE, [EI·R] is a reversibly formed complex between reactivator and phosphonylated AChE, E is active enzyme, [E·R] is a reversibly formed (inactive) complex between AChE and reactivator, and HOX is the protonated form (oxime) of added test compound.

Following the general procedure described earlier,[19,26] the enzyme activities in the presence of each type **3** test compound were determined. In the absence of EPMP, test compounds inhibited AChE in a reversible, time-inde-

(24) Ashani, Y.; Edery, H.; Zahavy, J.; Kungberg, W.; Cohen, S. *Israel J. Chem.* **1965**, *3*, 133.
(25) Michael, H. O.; Hackley, B. E.; Berkowitz, G. L.; Hackley, E. B.; Gillian, W.; Pandau, M. *Archiv. Biochem. Biophys.* **1967**, *121*, 29.
(26) Kenley, R. A.; Howd, R. A.; Mosher, C. W.; Winterle, J. S. *J. Med. Chem.* **1981**, *24*, 1124.
(27) Kenley, R. A.; Bedford, C. D.; Howd, R. A.; Dailey, O. D.; Miller, A. *J. Med. Chem.* **1984**, *27*, 1201.
(28) Bedford, C. D.; Howd, R. A.; Kenley, R. A.; Winterle, J. S.; Kern, J.; Dailey, O. D.; Miller, A.; Nolen, H. W. *J. Med. Chem.* **1986**, *29*, 2174.
(29) Bedford, C. D.; Miura, M.; Bottaro, J. C.; Howd, R. A.; Nolen, H. W. *J. Med. Chem.* **1986**, *29*, 1689.

Table I. Selected Physicochemical Data for 1-[(Alkenyloxy)methyl]-, 1-[(Alkynyloxy)methyl]-, and 1-[Aralkyloxy)methyl]-2-[(hydroxyimino)methyl]-3-methylimidiazolium Halides



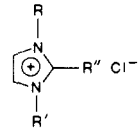
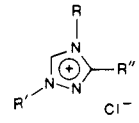
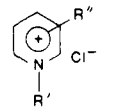
compd[a]	structure R	structure R′	mp, °C	yield,[b] %	pK_a[c]	log P[d]	formula[e]
			Alkenyl				
2a	CH_3	$CH_2CH{=}CH_2$	120–121.5	93	8.04	−2.50	$C_9H_{14}N_3O_2Cl$
2b	CH_3	$CH_2C(CH_3){=}CH_2$	137–138	58	7.99	−1.83	$C_{10}H_{16}N_3O_2Cl$
2c	CH_3	$C(CH_3)_2CH{=}CH_2$	117–118	37	7.94	−1.54	$C_{11}H_{18}N_3O_2Cl$
2d	CH_3	$CH_2CH{=}CHCH_3(t)$	85–86	31	8.07	−1.54	$C_{10}H_{16}N_3O_2Cl$
2e	CH_3	$CH_2CH{=}CHCH_3(c)$	130–131	49	8.04	−1.93	$C_{10}H_{16}N_3O_2Cl$
2f	CH_3	$CH_2CH{=}CHCH_2CH_3(t)$	109–110	61	8.00	−1.30	$C_{11}H_{18}N_3O_2Cl$
2g	CH_3	$CH_2CH{=}CHCH_2CH_3(c)$	114–115	53	8.06	−1.40	$C_{11}H_{18}N_3O_2Cl$
2h	CH_3	$CH_2CH{=}CHCH_2CH_2CH_3(t)$	115–116	83	8.00	−0.70	$C_{12}H_{20}N_3O_2Cl$
2i	CH_3	$CH_2CH{=}C(CH_3)_2$	128–129	44	8.04	−1.40	$C_{11}H_{18}N_3O_2Cl$
2j	CH_3	$CH_2CH{=}CHC(CH_3)_3$	138–140	43	8.04	−0.47	$C_{13}H_{22}N_3O_2Cl$
2k	CH_3	$CH(CH_2CH_2CH_3)CH{=}CH_2$	144–145	39	7.99	−0.87	$C_{12}H_{20}N_3O_2Cl$
2l	CH_3	$CH_2CH_2CH{=}CH_2$	115–116	55	7.97	−1.84	$C_{10}H_{16}N_3O_2Cl$
2m	CH_3	$CH_2CH_2CH{=}CHCH_2CH_3(t)$	120–122	43	7.99	−0.76	$C_{12}H_{20}N_3O_2Cl$
2n	CH_3	$CH_2CH_2C(CH_3){=}CH_2$	101–102	35	8.03	−1.41	$C_{11}H_{18}N_3O_2Cl$
2o	CH_3	$CH(C(CH_3){=}CH_2)CH_2C(CH_3){=}CH_2$	142–143	37	7.91	−0.62	$C_{14}H_{22}N_3O_2Cl$
			Alkynyl				
3a	CH_3	$CH_2C{\equiv}CH$	169–170	84	8.01	−2.90	$C_9H_{12}N_3O_2Cl$
3b	CH_3	$CH(CH_3)C{\equiv}CH$	150–152	95	7.96	−2.14	$C_{10}H_{14}N_3O_2Cl$
3c	CH_3	$C(CH_3)_2C{\equiv}CH$	138–140	50	7.98	−1.62	$C_{11}H_{16}N_3O_2Cl$
3d	CH_3	$C(CH_3)_2C{\equiv}CCH_3$	130.5–132	48	7.96	−1.36	$C_{12}H_{18}N_3O_2Cl$
3e	CH_3	$CH(CH_3)C{\equiv}CCH_3$	136–137	48	8.03	−1.74	$C_{11}H_{16}N_3O_2Cl$
3f	CH_3	$CH(CH_2CH_3)C{\equiv}CH$	177–179	53	7.99	−1.49	$C_{11}H_{16}N_3O_2Cl$
3g	CH_3	$CH(CH_2CH_2CH_3)C{\equiv}CH$	147–148	68	8.02	−1.10	$C_{12}H_{18}N_3O_2Cl$
3h	CH_3	$CH_2CH_2C{\equiv}CH$	128–129	83	7.99	−2.36	$C_{10}H_{14}N_3O_2Cl$
3i	CH_3	$CH_2CH_2C{\equiv}CCH_3$	153–154	71	8.04	−1.99	$C_{11}H_{16}N_3O_2Cl$
3j	CH_3	$CH(CH_3)CH_2C{\equiv}CH$	135–137	57	8.03	−2.10	$C_{11}H_{16}N_3O_2Cl$
3k	CH_3	$CH(CH_3)CH(CH_3)C{\equiv}CH$	133–135	57	8.00	−1.55	$C_{12}H_{18}N_3O_2Cl$
3l	CH_3	$CH(CH_2CH_2CH_3)CH_2C{\equiv}CH$	121–123	51	7.92	−1.17	$C_{13}H_{20}N_3O_2Cl$
3m	CH_3	$CH_2CH_2CH_2C{\equiv}CH$	113–114	70	8.20	−2.10	$C_{11}H_{16}N_3O_2Cl$
3n	CH_3	C_6H_{10}(2-C≡CH)	171–172	74	8.03	−1.70	$C_{14}H_{20}N_3O_2Cl$
3o	CH_3	C_5H_8(1-C≡CH)	154–155	56	7.97	−0.99	$C_{13}H_{18}N_3O_2Cl$
			Aralkyl				
4a	CH_3	$CH_2C_6H_5$	124–127	40	7.94	−1.30	$C_{13}H_{16}N_3O_2Cl$
4b	CH_3	$CH_2C_{10}H_7$(1)	125–128	60	8.11	−0.36	$C_{17}H_{18}N_3O_2Cl$
4c	CH_3	$CH_2C_{10}H_{11}$(1)	109–111	55	8.13	+0.07	$C_{17}H_{22}N_3O_2Cl$
4d	CH_3	CH_2(4-$CF_3C_6H_4$)	143–144	72	8.06	−0.18	$C_{14}H_{15}N_3O_2ClF_3$
4e	CH_3	CH_2(4-FC_6H_4)	138–140	49	7.98	−1.12	$C_{13}H_{15}N_3O_2ClF$
4f	CH_3	CH_2CH_2(2-$CF_3C_6H_4$)	140	45	8.13	−0.21	$C_{15}H_{17}N_3O_2ClF_3$
4g	CH_3	$CH(CH_2CH_2CH_3)C_6H_5$	128–130	32	8.03	−0.13	$C_{16}H_{22}N_3O_2Cl$
4h	CH_3	$CH_2CH_2CH_2C_6H_5$	130–131	82	8.05	−0.45	$C_{15}H_{20}N_3O_2Cl$
4i	CH_3	$CH_2CH_2CH_2CH_2C_6H_5$	126–128	76	8.05	−0.04	$C_{16}H_{22}N_3O_2Cl$
4j	CH_3	$CH(C_5H_9)C_6H_5$	122–124	48	8.03	+0.38	$C_{18}H_{24}N_3O_2Cl$
4k	CH_3	$CH_2CH{=}CHC_6H_5$	133–135	45	8.01	−0.55	$C_{15}H_{18}N_3O_2Cl$
4l	CH_3	$CH_2CH(CH_3)C{\equiv}CC_6H_5$	136–137	34	7.99	−0.05	$C_{17}H_{20}N_3O_2Cl$
4m	CH_3	$CH(CH_2CH_3)C{\equiv}CC_6H_5$	148–149	33	8.06	+0.31	$C_{17}H_{20}N_3O_2Cl$
4n	CH_3	$CH(CH(CH_3)_2)C{\equiv}CC_6H_5$	170–171	65	8.06	+0.71	$C_{18}H_{22}N_3O_2Cl$
4o	CH_3	$CH(CH_2CH_3)CH_2C{\equiv}CC_6H_5$	156–157	33	8.07	+0.21	$C_{18}H_{22}N_3O_2Cl$
4p	CH_3	$CH(C_6H_5)CH_2C{\equiv}CH$	151–152	53	7.99	−1.05	$C_{16}H_{18}N_3O_2Cl$

[a] See text for synthesis methods. [b] Yield for production of target compounds from immediate precursor. Yields were not optimized. [c] Determined spectrophotometrically in 0.1 M phosphate buffer. [d] Log P is the octanol buffer partition coefficient for 0.1 M, pH 7.6, phosphate buffer. [e] All compounds were analyzed for C, H, N, and Cl; analytical results were within ±0.4% of the theoretical values.

pendent fashion. The reactivator–AChE inhibition was expressed as the IC_{50}, i.e., the concentration of test compound that contributes to 50% AChE activity. Table III summarizes data for AChE inhibition of human AChE and shows that type 3 compounds as well as other selected alkynyl- and (alkynyloxy)methyl-substituted test compounds are moderate to strong reversible inhibitors highly dependent upon structural features.

Reactivation of EPMP-Phosphonylated Human AChE. Human erythrocyte (RBC) AChE was inhibited with EPMP and the kinetics of AChE reactivation as a function of the concentration of the added test compound investigated. With test compound added in excess over EPMP-inhibited enzyme, pseudo-first-order reactivation kinetics were observed. Following the previously derived kinetic treatment,[19] it is convenient to express reactivation potency as k_{OX} (= k_r/K_r), the bimolecular rate constant for reactivation in the limit of low reactivator concentration ([OX] ≪ K_r), and k_{HOX} as the product of k_{OX} and the fraction of added test compound present as oximate at pH

Table II. Selected Physicochemical Data on Alkynyloxy- and Alkynyl-Substituted Imidazolium, Triazolium, and Pyridinium Aldoximes

compd[a]	structure R	R′	R″	mp, °C	yield,[b] %	pK_a[c]	log P[d]	formula[e]
								
5	CH_3	$(CH_2)_4C{\equiv}CH$	CHNOH	127–128.5	72	8.18	−2.02	$C_{11}H_{16}N_3OCl$
6	$C(CH_3)_3$	$(CH_2)_4C{\equiv}CH$	CHNOH	170–170.5	69	8.06	−1.42	$C_{14}H_{22}N_3OCl$
7	CH_2OCH_3	$(CH_2)_4C{\equiv}CH$	CHNOH	117.5–118	63	8.23	−1.71	$C_{12}H_{18}N_3O_2Cl$
8	$C(CH_3)_3$	$CH_2OCH_2CH_2C{\equiv}CH$	CHNOH	140–142	93	7.84	−1.84	$C_{13}H_{20}N_3O_2Cl$
9	CH_3	$CH_2OCH_2CH{=}C{=}CH_2$	CHNOH	149–150	40	8.03	*f*	$C_{10}H_{14}N_3O_2Cl$
10	CH_3	$CH_2OCH_2CH_2C{\equiv}CH$	CH_3	121–123	46			$C_{10}H_{15}N_2OCl$
								
11	CH_3	$(CH_2)_4C{\equiv}CH$	CHNOH	147–148	45	7.34	−1.56	$C_{10}H_{15}N_4OCl$
								
12		$CH_2OCH_2CH_2C{\equiv}CH$	CHNOH(4)	143–143.5	76	8.18	−2.72	$C_{11}H_{13}N_2O_2Cl$
13		$(CH_2)_4C{\equiv}CH$	CHNOH(4)	191–192	93	8.36	−2.32	$C_{12}H_{15}N_2OCl$
14		$(CH_2)_4C{\equiv}CH$	CHNOH(2)	163–164	60	7.93	−1.94	$C_{12}H_{15}N_2OCl$

[a] See text for synthesis methods. [b] Yield for production of target compounds from immediate precursor. Yields were not optimized. [c] Determined spectrophotometrically in 0.1 M phosphate buffer. [d] Log P is the octanol buffer partition coefficient for 0.1 M, pH 7.6, phosphate buffer. [e] All compounds were analyzed for C, H, N, and Cl; analytical results were within ±0.4% of the theoretical values. [f] Not determined in present study.

Table III. Kinetic Constants for Reactivation of EPMP-Inhibited Human AChE by (Alkynyloxy)methyl Quaternarized Imidazolium, Triazolium, and Pyridinium Halides

compd[a]	IC_{50},[b] μM	$10^{-3}k_r$,[c] $min^{-1} \times 10^3$	$10^{-5}K_r$,[d] $M \times 10^5$	k_{OX},[e] M^{-1} min^{-1}	k_{HOX},[f] M^{-1} min^{-1}
3a	21.8	20.3	4.74	428	122
3b	11.9	9.96	1.61	618	176
3c	24.2	13.0	3.12	415	118
3d	175.0	4.62	2.54	182	51
3e	144.0	14.3	4.05	353	101
3f	7.81	19.9	4.04	492	140
3g	8.27	6.60	0.81	817	233
3h	14.5	3.54	0.82	433	125
3i	76.8	4.42	1.31	337	89
3j	8.72	4.89	0.84	583	166
3k	12.7	2.25	0.44	511	145
3l	5.21	1.42	0.36	391	111
3m	27.9	5.06	0.67	753	214
3n	20.3	7.39	0.86	853	243
3o	24.2	11.1	0.91	1217	347
5	8.5	13.8	1.02	1347	384
6	76.6	6.11	1.89	323	92
7	185.0	13.5	3.09	438	125
8	339.0	29.0	21.7	133	38
10	27.0	0.0	0.0	0	0
11	62.5	7.30	3.69	198	56
12	96.5	77.7	5.03	1546	440
13	305.0	29.0	1.63	1780	507
14	61.5	11.7	1.19	980	279
2-PAM	366.0			1695	482

[a] See Tables I and II for structures. [b] IC_{50} is the concentration of drug HOX that reversibly inhibits 50% of AChE activity. [c] k_r defines the transformation of the [inhibited enzyme/oximate] complex to active enzyme, see eq 13, ref 19. [d] K_r defines the formation of the inhibited enzyme/oximate complex, see eq 15, ref 19. [e] k_{OX} is the bimolecular reactivation rate constant and was calculated from eq 15, ref 19. [f] k_{HOX} is the effective rate constant for reactivation, adjusted for the differences in oxime ionization at pH 7.6 and was calculated from eq 16, ref 19.

7.6. Table III summarizes data for reactivation of EPMP-inhibited human AChE by selected imidazolium test compounds. For comparison, the table also gives data for 2-PAM.

Comparing the reactivation kinetics (k_{HOX} for EPMP-inhibited human AChE) reveals general trends within the (alkynyloxy)methyl class of compounds. Against EPMP, type **3** compounds are potent reactivators highly dependent upon the (alkynyloxy)methyl side chain: k_{HOX} values varied from a low of 51.8 M^{-1} min^{-1} (**3d**) to a high of 347 M^{-1} min^{-1} (**3o**) for human AChE. Removal of the ether linkage, compound **5**, increases the reactivation potency to 384 M^{-1} min^{-1}. For human AChE, compound **5** is almost equipotent with the standard 2-PAM toward reactivation of inhibited enzyme. As with the previous imidazolium compounds, the in vitro reactivation potency is far below that of HI-6.[18]

Replacement of the acetylenic hydrogen by a methyl group reduces the reactivation potency toward EPMP-inhibited human AChE (i.e., the three pairs of reactivators **3h**/**3i**, **3c**/**3d**, and **3b**/**3e** show a 35.7, 66.2, and 75.4 M^{-1} min^{-1} reduction in the reactivation potencies, respectively). The IC_{50} of the test drugs increase upon introduction of a terminal methyl group onto the acetylenic moiety. For the simple (alkynyloxy)methyl compounds with terminal hydrogens, the IC_{50}s ranged from a low of 7.8 μM to a high of 27.2 μM. This is a very narrow range and indicates that type **3** compounds have a high reversible affinity for the enzyme active site.

The triazolium and pyridinium reactivators, compounds **11** through **14**, also demonstrated significant in vitro reactivation potencies toward EPMP-inhibited AChE, Table III. Compounds **12** and **13** showed in vitro reactivation potency comparable to that of 2-PAM. Finally, as would be expected, removal of the oxime moiety, compound **10**, resulted in the complete loss of in vitro reactivation potency.

Protective Effects in Vivo against Soman. The results of initial in vivo mouse evaluations against GD for the compounds reported in this study are shown in Table

Table IV. Survival of Mouse against 2 × LD_{50} of Soman[a]

compd[b]	LD_{50},[c] mM/kg	no. of surviving mice (test compound + 11.2 mg/kg of atropine sulfate)[d] $^1/_4LD_{50}$ test drug	$^1/_8LD_{50}$ test drug	$^1/_{16}LD_{50}$ test drug
		Alkenyloxy		
2a	0.52	4	3	0
2b	0.53	1	3	0
2d	0.26	0	0	0
2e	0.35	2	1	0
2f	0.61	1	0	0
2g	0.64	1	3	4
2h	0.15	0	3	0
2i	0.43	0	0	0
2j	0.31	1	0	0
2k	0.39	1	0	0
2n	0.43	3	2	0
2o	0.20	0	0	0
		Alkynyloxy		
3a	0.54	2	1	0
3b	0.27	0	4	1
3c	0.44	4	6	4
3e	0.51	0	0	0
3f	0.43	4	1	3
3g	0.33	5	1	0
3h	0.62	10	9	4
3i	0.91	2	0	0
3j	0.36	5	2	0
3k	0.27	9	e	1
3m	0.42	7	4	3
		Aralkyloxy		
4a	0.65	0	0	e
4b	0.86	1	1	e
4c	0.20	0	0	0
4d	1.30	0	0	2
4f	0.043	0	0	0
4g	0.11	1	0	0
4h	0.86	0	0	0
4i	0.37	0	0	0
4j	0.29	1	1	1
4k	0.86	0	0	0
4m	0.18	1	1	0
4n	0.27	2	4	1
		Miscellaneous Reactivators		
5	0.40	7	3	0
7	0.60	0	1	0
8	0.32	0	0	0
9	0.47	2	0	0
10	0.76	0	0	0
11	1.58	1	1	0
12	0.67	0	0	0
2-PAM	0.85	0	0	0
HI-6	4.50	9	10	9

[a] LD_{50} GD (plus 11.2 mg/kg atropine) ≃ 130 μg/kg in ~20 to 30 g mouse; without atropine, GD LD_{50} ≃ 98 μg/kg. [b] See Tables I and II for structures. [c] The 24-h LD_{50}s were determined intramuscularly (im) by using 5 to 7 dose groups with 5 animals per dose. The test oximes generally ranged in toxicity between 2-PAMCl (853 μmol/kg, im) and TMB-4 (224 μmol/kg, im). [d] 2-PAMCl was used as a base line. No mice survived after intoxication with 2 × LD_{50} GD followed immediately by coadministration of 25 mg/kg of 2-PAMCl (~$^1/_4$ LD_{50}) plus 11.4 mg/kg of atropine sulfate. The number recorded represents the number surviving after 24 h out of 10 subjects. Mice were challenged im with 2 × LD_{50} of soman and treated 10 s later with the indicated dose level of test oxime plus atropine sulfate (11.2 mg/kg). [e] Not determined.

IV. As Table IV demonstrates, numerous imidazolium oximes afford significant protection against the lethal effects of 2 × LD_{50} of soman. In all cases 2-PAM was used as the base-line standard. Against a 2 × LD_{50} challenge of GD, all mice treated with $^1/_4$ the LD_{50} of 2-PAM (approximately 25 mg/kg) expire. Similar results are obtained with lower 2-PAM dose levels.

It is apparent from Table IV that the most effective in vivo therapeutics are the unsaturated (alkynyloxy)methyl and alkynyl compounds (**3a–m** and **5**) with several compounds showing 50 to 100% survival rates at selected doses. One acetylene compound, **3h**, was found to be extremely effective with potencies of 40%, 90%, and 100% survival at the three dose levels tested (comparable to HI-6 on a molar level). In general, the (alkynyloxy)methyl compounds that demonstrate moderate to high in vivo activity also demonstrated significant in vitro activity against EPMP-inhibited human AChE. One critical structural feature emerges from the results in Table IV, only terminally unsubstituted acetylenes demonstrate high protective abilities. Replacement of the terminal hydrogen by either methyl (compounds **3d**, **3e**, and **3i**) or phenyl substituents (compounds **4m** and **4n**) significantly reduce in vivo potencies. Increasing the steric bulk around the acetylenic moiety also enhances the protective potency of the drug; a steady increases in protective ability is observed for the series **3a**, **3b**, and **3c** from 10% to 40% to 60% maximum survival, respectively.

Examination of the other unsaturated substituted quaternary imidazolium compounds shown in Table IV reveals that the (alkenyloxy)methyl compounds (**2a** through **2o**) and (aralkyloxy)methyl compounds (**4a** through **4n**) are, for the most part, ineffective in protecting against GD intoxication.

Replacing the ether linkage in compound **3h** by a methylene group, compound **5**, increased drug toxicity while slightly reducing the protective ability of the drug. Although both effects were negative with respect to developing improved therapeutics, compound **5** is impervious to aqueous hydrolysis, a problem experienced with all the alkoxymethyl heteroaromatic quaternary systems, particularly the Hagedorn oximes. It is apparent from these initial results that substituents on the heteroaromatic ring system substantially influence compound efficacy. The ability to design compounds resistant to aqueous hydrolysis, compound **5**, is a major step in developing a universal organophosphate antidote.

A series of structurally related analogues, compounds **6–14** were studied to further explore efficacy of the (alkynyloxy)methyl substituent. As shown in Table IV, changing the heteroaromatic ring system from imidazolium to triazolium or pyridinium while maintaining the (alkynyloxy)methyl or alkynyl substituent failed to give compounds that protect against GD intoxication, compounds **11–14**. Changing the alkyl portion on the imidazole ring from methyl, compound **3h**, to *tert*-butyl, compounds **6** and **8**, or methoxymethyl, compound **7**, also failed to give effective treatment drugs. Changing the alkynyloxy group to an allenic moiety, compound **9**, did nothing to improve compound efficacy. Removing the oxime functional group, compound **10**, gave a material that was ineffective in both in vivo and in vitro studies.

Compounds **3c**, **3h**, **3g**, and **3j** were also evaluated against a Tabun (GA) challenge. Against 2.54 × LD_{50} of GA these compounds demonstrated modest protection of, 80%, 60%, 30% and 20%, respectively, at dose levels of $^1/_4$ the LD_{50} of the drug plus 11.5 mg/kg of atropine sulfate. In all cases, 2-PAM was run as the base line. At this dose level of GA, all mice treated with atropine and 2-PAM died, when 2-PAM was administered at $^1/_4$ the LD_{50} (25 mg/kg). Since these compounds were quite effective against both GD and GA, their antidotal action may be general in treating organophosphorus intoxication.

Structure–Activity Relationships. The (alkynyloxy)methyl-substituted imidazolium compounds are the

most effective therapeutic imidazolium reactivators developed to date. For the majority of type 3 compounds, the k_{HOX} determined for EPMP-inhibited human AChE paralleled the in vivo potency in mice against a GD challenge. From the limited number of type 3 compounds tested, the following general trends have emerged. First, branching on the (alkynyloxy)methyl substituent tends to increase the protective ability of the drug toward GD intoxication (see the series of compounds **3a**, **3b**, and **3c** and **3a**, **3b**, **3f**, and **3g**). Second, the (alkynyloxy)methyl chain length plays a critical role in the protective nature of the drug (see compounds **3a**, **3h**, and **3m**). The maximum protective effect is achieved with a six-atom unit (hexynyl moiety). The protective potency of the imidazolium drugs falls off rapidly on either side of this optimum chain length. Thirdly, replacing the terminal acetylenic hydrogen with alkyl or aryl substituents dramatically reduces both in vitro reactivation potency and in vivo protective ability of the drug (see compounds **3h**/**3i**, **3b**/**3e**, and **3c**/**3d**/**4l**). For this series of unsaturated imidazolium drugs, incorporation of the acetylenic functional group strongly favors in vivo protection against GD intoxication.

We postulate that the improved potency of type 3 compounds results from an increase in the number and kinds of interactions between the drug and the AChE active site. The general design of an efficient reactivator is based upon a compound possessing both a potent nucleophile (the oximate anion) and some ability to coordinate with the enzyme active site. This coordination can be through hydrophobic, hydrophilic, Coulombic, or any combination of these interactions, to assist in positioning the reactivator in close proximity to the phosphonylated enzyme or to enhance interactions with the free enzyme that may significantly reduce the relative toxicity of the antagonist. For most reactivators, this results from interactions between the anionic regions of the enzyme active site and the quaternary portion of the reactivating drug. The [(alkynyloxy)methyl]imidazolium compounds meet these criteria of an efficient reactivator. In addition, type 3 compounds possess a critical third factor that may enhance drug efficacy, the ability to interact with the cationic region (the protonated imidazole ring of the histidine residue) of the enzyme active site.[30] The protonated histidine moiety interacts with the partial negative charge present in terminal acetylene compounds forming a bidentate-type interaction with the enzyme. This kind of interaction explains why replacing the terminal hydrogen with a methyl substituent substantially reduced both in vivo and in vitro drug potency.

Conclusions

A variety of monoquaternary unsaturated and aryl-substituted (alkoxymethyl)imidazolium aldoximes were prepared and evaluated for in vitro reactivation of ethyl methylphosphonylated human AChE and for in vivo potency in mice against GD. For EPMP-inhibited AChE, 2-(hydroxyimino)methyl acid dissociation constants along with steric interactions between oxime reactivators and enzyme substrate dictate the inherent reactivity. Incorporation of (alkynyloxy)methyl moieties on the imidazole ring enhance activity toward EPMP-inhibited AChE. For the unsaturated (alkynyloxy)methyl-substituted compounds, branching on the alkyl substituent had little influence on the in vitro reactivation potency toward EPMP-inhibited AChE.

HI-6 is still the most potent compound in protecting against GD, although the type 3 compounds described in this report approach the protection level of HI-6 against GD intoxication. Future work will concentrate on reducing drug toxicity and improving hydrolytic stability. If the protective action of these imidazolium compounds can be maintained while reducing compound toxicity, one should be able to prepare organophosphate therapeutics superior to HI-6. The good correlation between protective ability and reactivation potencies for type 3 compounds indicates that reactivation is the major mechanism of action for the (alkynyloxy)methyl-substituted imidazolium ring system. Finally, the significant protection afforded by the imidazolium oximes should be evaluated in other species and against other organophosphorus compounds before the full utility of these materials can be realized.

The in vitro and in vivo model systems studied to date are essential to unravel the complex interactions between drug design and therapeutic effectiveness. Further investigations will be required to optimize molecular parameters important for improved in vivo efficacy such as favorable tissue distribution, moderate metabolism rates, and improved therapeutic index. However, it is apparent from the current study that at least two mechanisms of action are operational with these imidazolium reactivators: the first involves steric factors that may retard phosphonylation of the enzyme and the second involves direct reactivation of the inhibited enzyme by what appears to be an enhanced bidentate interaction between reactivator and inhibited enzyme. In following papers, we will continue to explore these factors.

Experimental Details[31]

Physical and Biological Measurements. Reactivator pK_a values were determined spectrophotometrically in 0.1 M phosphate buffer by the method of Albert and Sargeant.[32] Octanol:water partition coefficients were determined spectrophotometrically by the method of Fujita et al.[33] The aqueous phase for all log P determinations was pH 7.4, 0.1 M phosphate buffer. Competitive inhibition of human AChE as well as reactivation of AChE after inhibition with EPMP were performed as described previously. In vitro and in vivo results were obtained as described in our previous publications.[18,19]

General Procedure for Preparing Alkyl/Aryl Chloromethyl Ethers.[21,22] Dry HCl gas was bubbled into an ice-cooled mixture of the appropriate alcohol, 1 equiv of *s*-trioxane, and benzene (5 mL/g of alcohol) at a rate that maintained the reaction temperature below 15 °C. The reactions were generally complete within 2.5 h, at which time two phases had formed. After the aqueous layer was separated, the benzene layer was dried over calcium chloride, nitrogen gas was bubbled through the mixture to remove HCl, and the mixture was distilled at atmospheric pressure to remove benzene. The remaining residue was distilled under reduced pressure to provide the pure chloromethyl ethers.

The properties of new chloromethyl ethers prepared by the above procedure are listed in Table V.

General Procedure for Preparing Methoxymethyl Ethers.[23] Methoxymethyl (MOM) ethers were prepared by reacting the appropriate alcohol with a slight excess of NaH (free from oil) in THF until hydrogen evolution had ceased. Heating was required to initiate reaction with tertiary alcohols. After the alkoxide slurry was cooled in an ice–water bath, 1 equiv of chloromethyl methyl ether was added dropwise. After being warmed to room temperature, the mixtures were stirred a minimum of 1 h, filtered through Celite, and concentrated at atmospheric pressure for volatile MOM ethers and under reduced pressure for heavier MOM ethers. Purification was achieved by

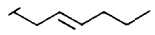
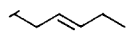
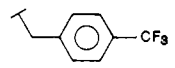
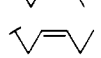
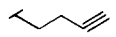
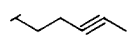
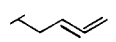
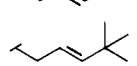
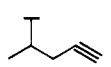
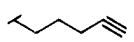
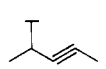
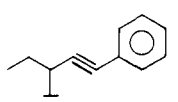
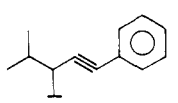
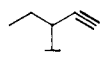
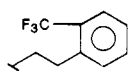
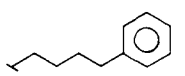
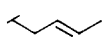
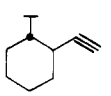
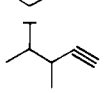
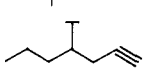
(30) Krupka, R. M.; Laidler, K. J. *J. Am. Chem. Soc.* **1961**, *83*, 1458.

(31) Instrumentation and materials used in the current study were described in detail in the Experimental Sections of ref 18 and 19.

(32) Albert, A.; Sargeant, E. P. *Ionization Constants of Acids and Basis*; J. Wiley and Sons: New York, 1968; p 49.

(33) Fujita, T.; Iwasa, J.; Hansch, C. *J. Am. Chem. Soc.* **1964**, *86*, 5175.

Table V. Selected Physicochemical Data for New Chloromethyl Ethers, $ClCH_2OR$, Prepared via General Procedure A

entry	R	% yield[b]	bp, °C (Torr)	$ClCH_2O$[c]	^1H NMR[a]: OR
a		13	44–47 (45)	5.68 (dd)	4.77 (dq, 1 H, CH), 2.53 (d, 1 H, CH), 1.52 (d, 3 H, CH_3)
b		43	86–91 (37)	5.56	4.30 (d, 2 H, CH_2), 2.13 (m, 2 H, CH_2), 1.43 (m, 2 H, CH_2), 0.87 (t, 3 H, CH_3)
c		57	70–75 (35)	5.60	6.0–5.3 (m, 2 H, CH), 4.20 (d, 2 H, CH_2), 2.05 (m, 2 H, CH_2), 1.00 (t, 3 H, CH_3)
d		41	125–132 (35)	5.60	7.65 (AB q, 4 H, aryl), 4.87 (s, 2 H, CH_2)
e		37	65–68 (50)	5.52	6.0–5.3 (m, 2 H, CH), 4.27 (d, 2 H, CH_2), 1.70 (d, 3 H, CH_3)
f		66	79–83 (67)	5.58	6.1–5.3 (m, 2 H, CH), 4.32 (d, 2 H, CH_2), 2.16 (m, 2 H, CH_2), 1.03 (t, 3 H, CH_3)
g		49	80–84 (80)	5.60	3.83 (t, 2 H, CH_2), 2.53 (dt, 2 H, CH_2), 2.07 (t, 1 H, CH)
h		28	97–115 (85)	5.63	3.73 (t, 2 H, CH_2), 2.73–2.26 (m, 2 H, CH_2), 1.77 (t, 3 H, CH_3)
i		49	71–75 (65)	5.60	5.36 (t, 1 H, CH), 5.20–4.80 (m, 2 H, CH), 4.35 (m, 2 H, CH_2)
j		78	53–55 (1.0)	5.60	6.0–5.53 (m, 2 H, CH), 4.26 (d, 2 H, CH_2), 1.06 (s, 9 H, CH_3)
k		47	71–75 (50)	5.62	4.08 (m, 1 H, CH), 2.60–2.33 (m, 2 H, CH_2), 2.05 (t, 1 H, CH), 1.33 (d, 3 H, CH_3)
l		65	88–90 (55)	5.56	3.82 (br t, 2 H, CH_2), 2.5–1.5 (m, 5 H, CH_2/CH)
m		66	75–77 (50)	5.68 (AB q)	4.63 (m, 1 H, CH), 1.87 (d, 3 H, CH_3), 1.45 (d, 3 H, CH_3)
n		63	104–106 (0.25)	5.75 (AB q)	7.40 (br s, 5 H, aryl), 4.76 (t, 1 H, CH), 1.90 (m, 2 H, CH_2), 1.10 (t, 3 H, CH_3)
o		57	94–98 (0.1)	5.73 (AB q)	7.34 (m, 5 H, aryl), 4.58 (d, 1 H, CH), 2.37–1.64 (m, 1 H, CH), 1.07 (d, 6 H, CH_3)
p		45	54–55 (40)	5.67 (AB q)	4.52 (td, 1 H, CH), 2.52 (d, 1 H, CH), 1.85 (m, 2 H, CH_2), 1.03 (t, 3 H, CH_3)
q		81	72–72 (0.15)	5.47	7.80–7.10 (m, 4 H, aryl), 3.93 (t, 2 H, CH_2), 3.13 (t, 2 H, CH_2)
r		82	79–80 (0.25)	5.45	7.20 (s, 5 H, aryl), 3.65 (t, 2 H, CH_2), 2.60 (br t, 2 H, CH_2), 1.65 (m, 4 H, CH_2)
s		35	60–63 (50)	5.50	6.20–5.23 (m, 2 H, CH), 4.13 (br d, 2 H, CH_2), 1.73 (br d, 3 H, CH_3)
t		62	112–114 (21)	5.70 (d of AB q)	3.90–3.50 (m, 1 H, CH), 2.12 (d, 1 H, CH), 2.67–0.70 (m, 9 H, cyclohexyl)
u		58	75–85 (55)	5.58	3.83 (q, 1 H, CH), 2.95–2.42 (m, 1 H, CH), 2.13 (d, 1 H, CH), 1.35 (d, 3 H, CH_3), 1.23 (d, 3 H, CH_3)
v		53	83–88 (18)	5.65	3.93 (q, 1 H, CH), 2.50 (dd, 2 H, CH_2), 2.05 (t, 1 H, CH), 1.85–1.10 (m, 4 H, CH_2), 1.10–0.75 (m, 3 H, CH_3)

[a] 60 MHz in $CDCl_3$ solvent. Shift values are reported in δ units relative to tetramethylsilane. [b] Refers to the distilled yield. [c] Unless otherwise noted, all $ClCH_2O$ protons appeared as a sharp singlet.

distillation. The properties of all new MOM ethers prepared by the above procedure are listed in Table VI.

General Procedure for Preparing Chloromethyl Ethers from MOM Ethers.[23] The MOM ethers in pentane were cooled to 0 °C, treated with 0.33 equiv of a 1.0 M solution of BCl_3 in hexane (Aldrich), and allowed to warm to room temperature to prepare the chloromethyl ethers. As monitored by ^1H NMR the reactions were generally complete within 1 h. Solvent and trimethylborate were removed under reduced pressure and vacuum distillation provided the pure chloromethyl ethers. The physicochemical properties of all new chloromethyl ethers prepared by the above procedure are listed in Table VI.

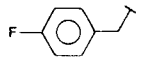
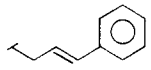
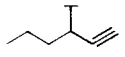
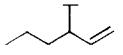
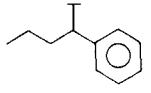
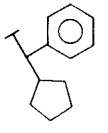
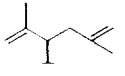
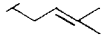
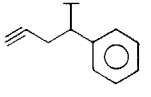
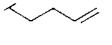
General Procedure for Synthesis of Imidazolium Salts. The imidazolium salts **2**, **3**, and **4** were prepared by dissolving 2-[(hydroxyimino)methyl]-1-methylimidazole[19] in THF–DMF (5:1) and adding 1.2 to 1.5 equiv of the appropriate chloromethyl ether. The reactions were generally complete after being stirred overnight. The solid precipitates were filtered, washed with ether, dried in vacuo, and recrystallized. The following type **2**, **3**, and **4** compounds were prepared by this method.

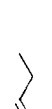
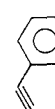
1-[(Allyloxy)methyl]-2-[(hydroxyimino)methyl]-3-methylimidazolium chloride (2a) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and allyl chloromethyl ether.

2-[(Hydroxyimino)methyl]-3-methyl-1-[[(2′-methyl-2′-propen-1′-yl)oxy]methyl]imidazolium chloride (2b) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 2-methyl-2-propen-1-yl ether.

2-[(Hydroxyimino)methyl]-3-methyl-1-[[(2′-methyl-3′-buten-2′-yl)oxy]methyl]imidazolium chloride (2c) was prepared

Table VI. Selected Physicochemical Data for New MOM Ethers, CH_3OCH_2OR, and Chloromethyl Ethers, $ClCH_2OR$, Prepared via General Procedure B

		MOM ether					chloromethyl ether			
				^1H NMR[b]					^1H NMR[b]	
entry	R	% yield[a]	bp, °C (Torr)	CH_3O	OCH_2O[c]	OR	% yield	bp, °C (Torr)	$ClCH_2O$[c]	OR
a		70	55–56 (0.4)	3.42	4.73	7.5–6.9 (m, 4 H, aryl), 4.58 (s, 2 H, CH_2)	41	57–59	5.55	7.53–7.03 (m, 4 H, aryl), 4.73 (s, 2 H, CH_2)
b		61	92–94 (0.25)	3.40	4.70	7.38 (br s, 5 H, aryl), 6.9–6.0 (m, 2 H, CH), 4.26 (AB q, 2 H CH_2)	50	73–78 (0.1)	5.58	7.43 (s, 5 H, aryl), 7.06–5.93 (m, 2 H, CH), 4.25 (d, 2 H, CH_2)
c		52	41–47 (75)	3.43	4.93	2.47 (s, 1 H, CH), 1.53 (s, 6 H, CH_3)	51	59–64 (70)	5.83	2.82 (s, 1 H, CH), 1.60 (s, 6 H, CH_3)
d		36	108–110	3.43	4.70	5.03–4.87 (m, 2 H, CH), 4.01 (s, 2 H, CH_2), 1.80 (s, 3 H, CH_3)	45	75–78 (120)	5.57	5.10 (m, 2 H, CH_2), 4.16 (s, 2 H, CH_2), 1.77 (s, 3 H, CH_2)
e		57	70–75 (45)	3.40	5.00, 4.65 (AB q)	4.75–4.15 (m, 1 H, CH), 2.45 (d, 1 H, CH), 2.00–1.45 (m, 4 H, CH_2), 1.00 (br t, 3 H, CH_3)	31	77–80 (45)	5.73, 5.60 (AB q)	4.7–4.3 (m, 1 H, CH), 2.52 (d, 1 H, CH), 1.85 (m, 4 H, CH_2), 1.0 (br t, 3 H, CH_3)
f		41	68–70 (50)	3.42	4.72, 4.52	6.05–5.00 (m, 3 H, CH/CH_2), 4.25 (m, 1 H, CH), 2.00–1.50 (m, 4 H, CH_2), 0.94 (br t, 3 H, CH_3)	74	74–75 (35)	5.46 (AB q)	6.0–5.1 (m, 3 H, CH/CH_2), 4.18 (m, 1 H, CH), 2.0–1.0 (m, 4 H, CH_2), 1.13–0.54 (br t, 3 H, CH_3)
g		74	74–75 (0.2)	3.37	4.53	7.30 (s, 5 H, aryl), 4.56 (t, 1 H, CH), 2.0–1.0 (m, 4 H, CH_2), 1.1–0.8 (m, 3 H, CH_3)	81	65–67 (0.15)	5.50, 5.13 (AB q)	7.33 (s, 5 H, aryl), 4.77 (t, 1 H, CH), 2.15–1.10 (m, 4 H, CH_2), 0.95 (m, 3 H, CH_3)
h		65	107–109 (0.15)	3.40	4.53	7.38 (s, 5 H, aryl), 4.34 (d, 1 H, CH), 2.6–1.0 (m, 9 H, cyclopentyl)	60	90–99 (0.1)	5.53, 5.12 (AB q)	7.28 (s, 5 H, aryl), 3.85 (d, 1 H, CH), 2.73–0.85 (m, 9 H, cyclopentyl)
i		76	88–92 (42)	3.37	4.60 (d of AB q)	5.10–4.70 (m, 4 H, CH_2), 4.20 (t, 1 H, CH), 2.43–1.07 (m, 2 H, CH_2), 1.77 (s, 3 H, CH_3), 1.70 (s, 3 H, CH_3)	56	65–68 (2.8)	5.45 (d of AB q)	5.10 (br s, 2 H, CH_2), 4.83 (br s, 2 H, CH_2), 4.40 (t, 1 H, CH), 2.47–2.03 (m, 2 H, CH_2), 1.77 (s, 3 H, CH_3), 1.67 (s, 3 H, CH_3)
j		43	62–66 (42)	3.37	4.63	5.83 (m, 1 H, CH), 4.06 (d, 2 H, CH_2), 1.73 (d, 6 H, CH_3)	43	66–67 (35)	5.55	5.37 (m, 1 H, CH), 4.27 (d, 2 H, CH_2), 1.78 (d, 6 H, CH_3)
k		60	77–80 (0.15)	3.40	4.60	7.33 (s, 5 H, aryl), 4.80 (t, 1 H, CH), 2.67 (dt, 2 H, CH_2), 2.00 (t, 1 H, CH)	61	81–82 (0.1)	5.40 (AB q)	7.40 (s, 5 H, aryl), 5.00 (t, 1 H, CH), 2.57 (dd, 2 H, CH_2), 2.00 (t, 1 H, CH)
l		81	86–87 (15)	3.40	4.77	5.90 (m, 1 H, CH), 5.23 (m, 1 H, CH), 5.00 (m, 1 H, CH), 3.65 (m, 2 H, CH_2), 1.33 (s, 6 H, CH_3)	47	47–48 (20)	5.55	6.00 (m, 1 H, CH), 5.38 (m, 1 H, CH), 5.17 (m, 1 H, CH), 1.40 (s, 6 H, CH_3)
m		50	39–40 (32)	3.40	4.67	5.80 (m, 1 H, CH), 5.22 (m, 1 H, CH), 4.94 (dm, 1 H,	66	52–58 (50)	5.53	6.01 (m, 1 H, CH), 5.24 (m, 1 H, CH), 5.05 (m, 1 H,

n		63	75–76 (16)	3.40	4.90	2.53 (s, 1 H, CH), 2.30–1.30 (m, 8 H, cyclopentyl), 2.37 (q, 2 H, CH_2)	76	84–86 (19)	5.77	2.67 (s, 1 H, CH), 2.40–1.50 (m, 8 H, cyclopentyl), 3.63 (t, 2 H, CH_2), 2.40 (q, 2 H, CH_2)
o		66	67–70 (35)	3.40	4.92	1.87 (s, 3 H, CH_3), 1.50 (s, 6 H, CH_3)	76	58–65	5.77	1.88 (s, 3 H, CH_3), 1.53 (s, 6 H, CH_3), 3.63 (t, 2 H, CH_2), 2.37 (q, 2 H, CH_2)
p		56	84–85 (80)	3.37	4.67	5.63–5.33 (m, 2 H, CH), 3.53 (t, 2 H, CH_2), 2.50–1.73 (m, 4 H, CH_2), 0.97 (t, 3 H, CH_3)	67	84–85 (25)	5.56	5.85–5.41 (m, 2 H, CH_2), 3.77 (t, 2 H, CH_2), 2.57–1.77 (m, 4 H, CH_2), 1.00 (t, 3 H, CH_3), 3.63 (t, 2 H, CH_2), 2.37 (q, 2 H, CH_2)
q		64	109–111 (0.2)	3.42	4.77	7.32 (m, 5 H, aryl), 3.73 (q, 1 H, CH), 2.65 (d, 2 H, CH_2), 1.68 (m, 2 H, CH_2), 0.98 (t, 3 H, CH_3)	83	112–114 (0.2)	5.68 (d of AB q)	7.35 (m, 5 H, aryl), 3.94 (q, 1 H, CH), 2.72 (d, 2 H, CH_2), 1.70 (m, 2 H, CH_2), 1.00 (t, 3 H, CH_3), 3.63 (t, 2 H, CH_2), 2.37 (q, 2 H, CH_2)
r		61	82–83 (0.25)	3.47	4.06	7.40 (s, 5 H, aryl), 1.65 (s, 6 H, CH_3)	71	84–88 (0.25)	5.80	7.40 (br s, 5 H, aryl), 1.67 (s, 6 H, CH_3), 3.63 (t, 2 H, CH_2), 2.37 (q, 2 H, CH_2)

[a] Refers to the isolated distilled yield. [b] 60 MHz in $CDCl_3$ solvent. Shift values are reported in δ units relative to tetramethylsilane. [c] Unless otherwise noted all $ClCH_2O$ and OCH_2O protons appeared as a sharp singlet.

from chloromethyl (2-methyl-3-buten-2-yl ether and 2-[(hydroxyimino)methyl]-1-methylimidazole.

1-[(2′(*E*)-Buten-1′-yloxy)methyl]-2-[(hydroxyimino)methyl]-3-methylimidazolium chloride (2d) was prepared from chloromethyl 2(*E*)-buten-1-yl ether and 2-[(hydroxyimino)methyl]-1-methylimidazole.

1-[(2′(*Z*)-Buten-1′-yloxy)methyl]-2-[(hydroxyimino)methyl]-3-methylimidazolium chloride (2e) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and 2(*Z*)-buten-1-yl chloromethyl ether.

2-[(Hydroxyimino)methyl]-3-methyl-1-[(2′(*E*)-penten-1′-yloxy)methyl]imidazolium chloride (2f) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 2(*E*)-penten-1-yl ether.

2-[(Hydroxyimino)methyl]-3-methyl-1-[(2′(*Z*)-penten-1′-yloxy)methyl]imidazolium chloride (2g) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 2(*Z*)-penten-1-yl ether.

1-[(2′(*E*)-Hexen-1′-yloxy)methyl]-2-[(hydroxyimino)methyl]-3-methylimidazolium chloride (2h) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 2(E)-hexen-1-yl ether.

2-[(Hydroxyimino)methyl]-1-[[(3′-methyl-2′-buten-1′-yl)oxy]methyl]-3-methylimidazolium chloride (2i) was prepared from chloromethyl 3-methyl-2-buten-1-yl ether and 2-[(hydroxyimino)methyl]-1-methylimidazole.

1-[[(4′,4′-Dimethyl-2′-penten-1′-yl)oxy]methyl]-2-[(hydroxyimino)methyl]-3-methylimidazolium chloride (2j) was prepared from (chloromethyl 4,4-dimethyl-2-penten-1-yl ether and 2-[(hydroxyimino)methyl]-1-methylimidazole.

1-[(1′-Hexen-3′-yloxy)methyl]-2-[(hydroxyimino)methyl]-3-methylimidazolium chloride (2k) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 1-hexen-3-yl ether.

1-[(3′-Buten-1′-yloxy)methyl]-2-[(hydroxyimino)methyl]-3-methylimidazolium chloride (2l) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and 3-buten-1-yl chloromethyl ether.

1-[(3′-Hexen-1′-yloxy)methyl]-2-[(hydroxyimino)methyl]-3-methylimidazolium chloride (2m) was prepared from chloromethoxyl 3-hexen-1-yl ether and 2-[(hydroxyimino)methyl]-1-methylimidazole.

2-[(Hydroxyimino)methyl]-3-methyl-1-[[(3′-methyl-3′-buten-1′-yl)oxy]methyl]imidazolium chloride (2n) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and 4-[(chloromethyl)oxy]-2-methyl-1-butene.

1-[[(2′,5′-Dimethyl-1′,5′-hexadien-3′-yl)oxy]methyl]-2-[(hydroxyimino)methyl]-3-methylimidazolium chloride (2o) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 2,5-dimethyl-1,5-hexadien-3-yl ether.

2-[(Hydroxyimino)methyl]-3-methyl-1-[(2′-propyn-1′-yloxy)methyl]imidazolium chloride (3a) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 2-propyn-1-yl ether.

1-[(3′-Butyn-2′-yloxy)methyl]-2-[(hydroxyimino)methyl]-3-methylimidazolium chloride (3b) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and 3-butyn-2-yl chloromethyl ether.

1-[[(1′,1′-Dimethyl-2′-propyn-1′-yl)oxy]methyl]-2-[(hydroxyimino)methyl]-3-methylimidazolium chloride (3c) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 2-methyl-3-butyn-2-yl ether.

2-[(Hydroxyimino)methyl]-3-methyl-1-[[(2′-methyl-3′-pentyn-2′-yl)oxy]methyl]imidazolium chloride (3d) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 2-methyl-3-pentyn-2-yl ether.

2-[(Hydroxyimino)methyl]-3-methyl-1-[(3′-pentyn-2′-yloxy)methyl]imidazolium chloride (3e) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 3-pentyn-2-yl ether.

2-[(Hydroxyimino)methyl]-3-methyl-1-[(1′-pentyn-3′-yloxy)methyl]imidazolium chloride (3f) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 1-pentyn-3-yl ether.

1-[(1′-Hexyn-3′-yloxy)methyl]-2-[(hydroxyimino)methyl]-3-methylimidazolium chloride (3g) was prepared from chloromethyl 1-hexyn-3-yl ether and 2-[(hydroxyimino)methyl]-1-methylimidazole.

1-[(3′-Butyn-1′-yloxy)methyl]-2-[(hydroxyimino)methyl]-3-methylimidazolium chloride (3h) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and 3-butyn-1-yl chloromethyl ether.

2-[(Hydroxyimino)methyl]-3-methyl-1-[(3′-pentyn-1′-yloxy)methyl]imidazolium chloride (3i) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 3-pentynyl ether.

2-[(Hydroxyimino)methyl]-3-methyl-[(4′-pentyn-2′-yloxy)methyl]imidazolium chloride (3j) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 4-pentyn-2-yl ether.

2-[(Hydroxyimino)methyl]-3-methyl-1-[[(3′-methyl-1′-pentyn-4′-yl)oxy]methyl]imidazolium chloride (3k) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and *erythro*-chloromethyl 3-methyl-4-pentyn-2-yl ether.

1-[(1′-Heptyn-4′-yloxy)methyl]-2-[(hydroxyimino)methyl]-3-methylimidazolium chloride (3l) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 1-heptyn-4-yl ether.

2-[(Hydroxyimino)methyl]-3-methyl-1-[(1′-pentyn-5′-yloxy)methyl]imidazolium chloride (3m) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 4-pent-1-yl ether.

1-[[(2′-Ethynylcyclohex-1′-yl)oxy]methyl]-2-[(hydroxyimino)methyl]-3-methylimidazolium chloride (3n) was prepared from chloromethyl 2-ethynylcyclohex-1-yl ether and 2-[(hydroxyimino)methyl]-1-methylimidazole.

1-[[(1′-Ethynylcyclopent-1′-yl)oxy]methyl]-2-[(hydroxyimino)methyl]-3-methylimidazolium chloride (3o) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 1-ethynylcyclopent-1-yl ether.

1-[(Benzyloxy)methyl]-2-[(hydroxyimino)methyl]-3-methylimidazolium chloride (4a) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and benzyl chloromethyl ether (Aldrich) and obtained as an off-white solid from EtOH.

2-[(Hydroxyimino)methyl]-3-methyl-1-[[(1′-methylnaphthyl)-1′-oxy]methyl]imidazolium chloride (4b) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 1-methylnaphthyl ether and obtained as a white solid from 2-propanol/EtOAc (1:1).

2-[(Hydroxyimino)methyl]-3-methyl-1-[[(1′,2′,3′,4′-tetrahydronaphth-1′-yl)methoxy]methyl]imidazolium chloride (4c) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl (1,2,3,4-tetrahydronaphth-1-yl)methyl ether and obtained as a white crystals of the hemihydrate from acetone/water (20:1).

2-[(Hydroxyimino)methyl]-3-methyl-1-[[[4′-(trifluoromethyl)benzyl]oxy]methyl]imidazolium chloride (4d) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 4′-(trifluoromethyl)benzyl ether.

1-[(4′-Fluorobenzyloxy)methyl]-2-[(hydroxyimino)methyl]-3-methylimidazolium chloride (4e) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 4-fluorobenzyl ether.

2-[(Hydroxyimino)methyl]-3-methyl-1-[[[2′-[2″-(trifluoromethyl)phenyl]ethyl]oxy]methyl]imidazolium chloride (4f) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 2-[2′-(trifluoromethyl)-phenyl]ethyl ether.

2-[(Hydroxyimino)methyl]-3-methyl-1-[[(1′-phenylbut-1′-yl)oxy]methyl]imidazolium chloride (4g) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 1-phenylbut-1-yl ether.

2-[(Hydroxyimino)methyl]-3-methyl-1-[[(3′-phenylprop-1′-yl)oxy]methyl]imidazolium chloride (4h) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 3-phenylpropyl ether and obtained as colorless crystals from 2-propanol.

2-[(Hydroxyimino)methyl]-3-methyl-1-[[(4′-phenylbut-1′-yl)oxy]methyl]imidazolium chloride (4i) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 4-phenylbut-1-yl ether.

1-[[[(1′-Cyclopentylphenyl)methyl]oxy]methyl]-2-[(hydroxyimino)methyl]-3-methylimidazolium chloride (4j) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl (cyclopentylphenyl)methyl ether.

2-[(Hydroxyimino)methyl]-3-methyl-1-[[(3′-phenyl-2′-(*E*)-propen-1′-yl)oxy]methyl]imidazolium chloride (4k) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 3-phenylprop-2(*E*)-en-1-yl ether.

2-[(Hydroxyimino)methyl]-3-methyl-1-[[(3′-methyl-1′-phenyl-1′-butyn-4′-yl)oxy]methyl]imidazolium chloride (4l) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 2-methyl-4-phenyl-3-butyn-2-yl ether.

2-[(Hydroxyimino)methyl]-3-methyl-1-[[(1′-phenyl-1′-pentyn-3′-yl)oxy]methyl]imidazolium chloride (4m) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 1-phenyl-1-pentyn-3-yl ether.

2-[(Hydroxyimino)methyl]-3-methyl-1-[[(4′-methyl-1′-phenyl-1′-pentyn-3′-yl)oxy]methyl]imidazolium chloride (4n) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 4-methyl-1-phenyl-1-pentyn-3-yl ether.

2-[(Hydroxyimino)methyl]-3-methyl-1-[[(1′-phenyl-1′-hexyn-4′-yl)oxy]methyl]imidazolium chloride (4o) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 1-phenyl-1-hexyn-4-yl ether.

2-[(Hydroxyimino)methyl]-3-methyl-1-[[(1′-phenyl-3′-butyn-1′-yl)oxy]methyl]imidazolium chloride (4p) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and chloromethyl 1-phenyl-3-butyn-1-yl ether.

5-Hexyn-1-yl Trifluoromethanesulfonate. An ice-cold mixture of 1.96 g (20.0 mmol) of 4-hexyn-1-ol and 1.62 mL (20.0 mmol) of pyridine in 14 mL of methylene chloride was added over 20 min to an ice–salt bath cooled solution of 3.38 mL (20.0 mmol) of trifluoromethanesulfonic anhydride in 20 mL of methylene chloride. The mixture was stirred for 20 min, washed twice with water, dried over $MgSO_4$, filtered, and evaporated in vacuo to afford 4.35 g of 5-hexyn-1-yl trifluoromethanesulfonate: bp 50 °C (0.5 Torr); ^1H NMR ($CDCl_3$) δ 4.62 (t, 2 H, J = 6 Hz, CH_2), and 2.50–1.50 ppm (m, 7 H, CH_2/CH_3).

1-(Hex-5′-yn-1′-yl)-2-[(hydroxyimino)methyl]-3-methylimidazolium Chloride (5). To 3.00 g (24.0 mmol) of 2-[(hydroxyimino)methyl]-1-methylimidazole in 100 mL of tetrahydrofuran was added 6.28 g (27.3 mmol) of 5-hexyn-1-yl trifluoromethanesulfonate in 23 mL of methylene chloride over 15 min with stirring at room temperature. The mixture was stirred for 1 h, and the solution was evaporated in vacuo. The residue was ion-exchanged [Amberlite IRA-400 (Cl^-)] to yield 7.52 g, which was recrystallized from ethanol/ethyl acetate to afford 5.06 g of the title compound as a colorless solid: ^1H NMR (DMSO-d_6) δ 12.12 (br, 1 H, NOH), 8.70 (s, 1 H, C*H*NOH), 8.11 (s, 2 H, aryl), 4.51 (t, 2 H, CH_2), 4.07 (s, 3 H, CH_3), and 2.79–1.41 ppm (m, 7 H, CH_2, acetylenic).

1-*tert*-Butylimidazole-2-carboxaldehyde. A solution of *tert*-butyl isothiocyanate (15.0 g, 0.13 mol) and aminoacetaldehyde diethyl acetal (17.2 g, 0.13 mol) in 300 mL of anhydrous ethanol was refluxed for 4 h. The solvent was removed under vacuum to give 32.5 g of a clear liquid. The NMR spectrum was consistent with the desired addition product; 1-*tert*-butyl-3-(2,2-diethoxyethyl)thiourea.

This intermediate was placed in 300 mL of 10% H_2SO_4 and refluxed overnight. The solution was cooled to 0 °C and the precipitate collected by filtration to yield 12.0 g of a crystalline solid having an NMR spectrum consistent with that expected for 1-*tert*-butyl-2-mercaptoimidazole. The mercaptoimidazole was dissolved in 500 mL of 10% HNO_3 in a 4-L Erlenmeyer flask to remove the sulfur. This reaction was initiated by either adding a few drops of concentrated HNO_3 to the solution at room temperature or by heating to reflux for 10–15 min. The resulting exothermic reaction liberates substantial quantities of NO_2 gas very rapidly and care must be taken to avoid boil overs. The reaction is completed within 5 min after initiation.

The reaction mixture was cooled, neutralized with $NaHCO_3$, and extracted with 3 × 200 mL portions of dichloromethane. The

organic layers were combined, dried over $MgSO_4$, and concentrated to remove the solvent, and the product was distilled under vacuum to give 7.10 g of *tert*-butylimidazole (44% overall yield): ^1H NMR ($CDCl_3$) δ 7.55 (s, 1 H, aryl), 6.98 (s, 2 H, aryl), and 1.51 ppm (s, 9 H, CH_3).

The imidazole dissolved in ether was added dropwise to a −50 °C solution of 1.1 equiv of lithium diisopropylamide in ether with stirring under argon. After the solution was stirred at −50 to −40 °C for 1 h, 1.5 equiv of dry DMF was added rapidly, and the mixture was allowed to warm to room temperature and then stirred for an additional hour. A saturated solution of sodium hydrogen phosphate (1.1 equiv) was added and the two phases were separated. The aqueous layer was extracted with two portions of ether and the combined ether layers were dried, concentrated, and distilled to give the aldehyde. 1-*tert*-Butylimidazole-2-carboxaldehyde was isolated in 94% yield as a colorless oil: bp 69–72 °C (0.4 Torr); ^1H NMR ($CDCl_3$) δ 9.93 (s, 1 H, CHO), 7.44 (s, 1 H, aryl), 7.32 (s, 1 H, aryl), and 1.72 ppm (s, 9 H, CH_3).

1-*tert*-Butyl-2-[(hydroxyimino)methyl]imidazole was isolated in 75% yield as white platelets after recrystallization from absolute ethanol: mp 152–155 °C; ^1H NMR (DMSO-d_6) δ 11.45 (br s, 1 H, NOH), 8.32 (s, 1 H, C*H*NOH), 7.41 (d, 1 H, aryl), 7.00 (d, 1 H, aryl), and 1.60 ppm (s, 9 H, CH_3).

3-*tert*-Butyl-1-(hex-5′-yn-1′-yl)-2-[(hydroxyimino)methyl]imidazolium Chloride (6). To an ice-cooled suspension of 6.0 g (35.9 mmol) of 2-[(hydroxyimino)methyl]-1-*tert*-butylimidazole in 120 mL of nitromethane was syringed 1.1 equiv of the hexynyl triflate. The solid dissolved as the triflate was added, the solution was allowed to warm to room temperature and stirred for 15 min before concentrating the mixture to a yellow oil. The oil was ion-exchanged [Amberlite IRA 400 (Cl^-)] to give a yellow solid, which was recrystallized in isopropyl alcohol to give 7.04 g of off-white crystals: ^1H NMR (DMSO-d_6) δ 12.95 (s, 1 H, NOH), 8.60 (s, 1 H, C*H*NOH), 8.10 (s, 2 H, aryl), 4.25 (t, 2 H, NCH_2), 2.84 (t, 1 H, acetylenic), 2.22 (dt, 2 H, CH_2), 1.64 (s, 9 H, CH_3), and 2.02–1.37 (m, 4 H, CH_2).

3-*tert*-Butyl-1-[(3′-butyn-1′-yloxy)methyl]-2-[(hydroxyimino)methyl]imidazolium chloride (8) was prepared from 2-[(hydroxyimino)methyl]-1-*tert*-butylimidazole and 3-butyn-1-yl chloromethyl ether yielding (93.3%) compound 8 as white crystals: ^1H NMR (DMSO-d_6) δ 13.05 (s, 1 H, NOH), 8.63 (s, 1 H, C*H*NOH), 8.17 (s, 2 H, aryl), 5.68 (s, 2 H, NCH_2O), 3.69 (t, 2 H, CH_2), 2.88 (t, 1 H, acetylenic), 2.47 (m, 2 H, CH_2) and 1.67 ppm (s, 9 H, CH_3).

1-(5′-Hexynyl)imidazole-2-carboxaldehyde Diethyl Acetal. To a continuously stirred mixture of 50 g (0.294 mol) of 1-(diethoxymethyl)imidazole[34] in 250 mL of THF cooled at −55 °C under Ar was added 124.4 mL of 2.6 M *n*-BuLi in hexanes dropwise over 45 min. After the mixture was stirred for 30 additional min at −50 °C to −55 °C, 35.9 g (0.49 mol) of dry DMF was added in one portion and the mixture was allowed to slowly warm to room temperature and stirred overnight. Then a solution of 44.6 g of $NaH_2PO_4 \cdot H_2O$ in 150 mL of water was added dropwise followed by 300 mL of EtOAc. The layers were separated and the aqueous layer was filtered and extracted well with EtOAc. All organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated to give a yellow oil. The oil was vacuum-distilled to give 42.9 g (74%) of 1-(diethoxymethyl)-2-formylimidazole as a colorless, oily solid: bp 78–82 °C (0.6 Torr); ^1H NMR ($CDCl_3$) δ 9.88 (s, 1 H, CHO), 7.61 (s, 1 H, aryl), 7.32 (s, 1 H, aryl), 7.00 (s, 1 H, CH), 3.65 (dq, 4 H, CH_2), 1.23 (t, 6 H, $2CH_3$).

The above aldehyde (42.8 g, 0.216 mol) was taken up in 2 L of absolute EtOH, treated with 1.15 mL of sulfuric acid, and heated at reflux for 28 h. The mixture was then cooled, the pH adjusted to 7 with 1 N NaOH, and concentrated to give a tan solid. The solid was taken up in CH_2Cl_2 and filtered free of unreacted aldehyde, and the filtrate was flash chromatographed over silica and eluted with CH_2Cl_2/EtOAc (1:1) to give 32.6 g (88.5%) of the diethyl acetal as white needles: mp 115–116 °C; ^1H NMR (DMSO-d_6) δ 6.94 (s, 2 H, aryl), 5.54 (s, 1 H, CH), 3.67 (q, 4 H, CH_2), 1.20 (t, 6 H, CH_3).

(34) Curtis, N. J.; Brown, R. S. *J. Org. Chem.* **1980**, *45*, 4038.

To a solution of 1.50 g (50 mmol) of 80% sodium hydride in 150 mL of THF was added 8.51 g (48 mmol) of the protected imidazole-2-carboxaldehyde in portions with stirring at 0 °C. When evolution of H_2 gas had ceased, 9.39 g (≤50 mmol) of 5-hexyn-1-yl trifluoromethanesulfonate in 30 mL of THF was added. The reaction mixture was stirred at room temperature for 16 h and the solvent evaporated in vacuo. The residue was extracted with ethyl acetate, washed with water, dried over anhydrous $MgSO_4$, filtered, and evaporated to yield 12.26 g of the crude imidazole adduct. The crude product was oximated without further purification: ^1H NMR ($CDCl_3$) δ 6.96 (s, 2 H, aryl), 5.55 (s, 2 H, CH_2), 4.19 (t, 2 H, J = 7 Hz, CH_2), 3.60 (q, 4 H, J = 7 Hz, CH_2), 2.24 (dt, 2 H, J = 7 Hz, CH_2), 2.00 (t, 1 H, J = 2 Hz, CH), and 1.23 ppm (t, 6 H, CH_3).

1-(Hex-5′-yn-1′-yl)-2-[(hydroxyimino)methyl]imidazole was isolated in 65.5% yield as a white colorless solid after recrystallization from ethyl acetate/hexane: mp 96.5–97 °C; ^1H NMR ($CDCl_3$) δ 11.30 (br s, 1 H, NOH), 8.35 (s, 1 H, C*H*NOH), 7.13 and 7.00 (two s, 2 H, aryl), 4.37 (t, 2 H, J = 7 Hz, CH_2), and 2.37–1.25 ppm (m, 7 H, CH_2 CH).

3-(Hex-5′-yn-1′-yl)-2-[(hydroxyimino)methyl]-1-(methoxymethyl)imidazolium Chloride (7). To 3.75 g (19.6 mmol) of 1-(hex-5′-yn-1′-yl)-2-[(hydroxyimino)methyl]imidazole in THF (60 mL) was added 1.64 mL (21.6 mmol) of chloromethyl methyl ether at 0 °C. The mixture was allowed to warm to room temperature and stirring continued for 5 h. The solvent was decanted away from 5.40 g of colorless oil. The salt, which solidified on cooling and vacuum, was crystallized from ethyl acetate/hexane to afford 3.38 g of 3-(hex-5′-yn-1′-yl)-2-[(hydroxyimino)methyl]-1-(methoxymethyl)imidazolium chloride as a colorless solid. ^1H NMR (DMSO-d_6) δ 12.65 (s, 1 H, NOH), 8.67 (s, 1 H, C*H*NOH), 8.33–8.16 (m, 2 H, aryl), 5.80 (s, 2 H, NCH_2O), 4.50 (t, 2 H, J = 7 Hz, CH_2), 3.38 (s, 3 H, CH_3), 2.85 (t, 1 H, J = 2 Hz, acetylenic) and 2.45–1.30 ppm (m, 6 H, CH_2).

1-[(1′,2′-Butadien-4′-yloxy)methyl]-2-[(hydroxyimino)methyl]-3-methylimidazolium chloride (9) was prepared from 2-[(hydroxyimino)methyl]-1-methylimidazole and buta-1,2-dien-4-yl chloromethyl ether and recrystallized from EtOAc/EtOH: ^1H NMR (DMSO-d_6) δ 12.63 (s, 1 H, NOH), 8.67 (s, 1 H, C*H*NOH), 8.20 and 8.12 (two d, 1 H each, aryl), 5.94 (s, 2 H, NCH_2O), 5.42 (q, 1 H, olefinic), 5.16–4.87 (m, 2 H, olefinic), 4.33–4.06 (m, 2 H, CH_2), and 4.05 ppm (s, 3 H, NCH_3).

1,2-Dimethyl-3-[(3′-butyn-1′-yloxy)methyl]imidazolium chloride (10) was prepared from 1,2-dimethylimidazole and 3-butynyl chloromethyl ether and recrystallized from EtOAc/EtOH: ^1H NMR (DMSO-d_6) δ 7.95 (br s, 1 H, aryl), 7.79 (br s, 1 H, aryl), 5.70 (s, 2 H, CH_2), 3.85 (s, 3 H, NCH_3), 3.58 (m, 2 H, CH_2), 2.89 (m, 1 H, CH), 2.67 (s, 3 H, CH_3) and 2.45 ppm (m, 2 H, CH_2).

1-(Hex-5′-yn-1′-yl)-3-[(hydroxyimino)methyl]-4-methyl-1,2,4-triazolium Chloride (11). To 3.78 g (30.0 mmol) of 3-[(hydroxyimino)methyl]-1-methyl-1,2,4-triazole in 125 mL of nitromethane was added 7.44 g (32.3 mmol) of 5-hexyn-1-yl trifluoromethanesulfonate at 0 °C. The mixture was allowed to warm to room temperature and stirring continued for 2 h. The solvent was evaporated in vacuo and the oil ion-exchanged [Amberlite IRA-400 (Cl^-)]. The resulting solid was recrystallized to afford 3.32 g (45.6%) of the product was a colorless solid: ^1H NMR (DMSO-d_6) δ 13.03 (br s, 1 H, NOH), 9.57 (s, 1 H, aryl), 8.80 (s, 1 H, C*H*NOH), 4.47 (t, 2 H, J = 7 Hz, NCH_2), 4.15 (s, 3 H, CH_3), 2.85 (t, 1 H, J = 2 Hz, acetylenic), and 2.45–1.30 ppm (m, 6 H, CH_2).

1-[(3′-Butyn-1′-yloxy)methyl]-4-[(hydroxyimino)methyl]pyridinium Chloride (12). To 3.66 g (30.0 mmol) of 4-pyridine aldoxime was added 3.91 g (3.30 mmol) of 3-butynyl chloromethyl ether at 0 °C. The cooling bath was removed and stirring continued for 5 h at room temperature. The solid was filtered and recrystallized from ethanol/ethyl acetate to afford 5.50 g of the product: ^1H NMR (DMSO-d_6) δ 12.35 (s, 1 H, NOH), 9.32 and 8.39 (two d, 4 H, J = 7 Hz, aryl), 8.57 (s, 1 H, C*H*NOH), 6.09 (s, 2 H, NCH_2), 3.77 (t, 2 H, J = 6 Hz, CH_2), 2.88 (t, 1 H, J = 3 Hz, acetylenic), and 2.70–2.35 ppm (m, 2 H, CH_2).

1-(Hex-5′-yn-1′-yl)-4-[(hydroxyimino)methyl]pyridinium Chloride (13). To 4.00 g (33.0 mmol) of 4-pyridine aldoxime in 125 mL of nitromethane at 0 °C was added 8.35 g (36.3 mmol) of 5-hexyn-1-yl trifluoromethanesulfonate neat over 10 min. After

0.5 h at 0 °C, the reaction was complete. The solvent was evaporated in vacuo to give a colorless oil, which was ion-exchanged [Amberlite IRA-400 (Cl^-)] to give a white solid. Recrystallization from ethanol/ethyl acetate gave 7.34 g of the title compound as a colorless solid: ^1H NMR (DMSO-d_6) δ 12.26 (s 1 H, NOH), 9.31 and 8.34 (two d, 4 H, J = 7 Hz, aryl), 8.55 (s, 1 H, C*H*NOH), 4.75 (t, 2 H, J = 7 Hz, NCH_2), 2.86 (t, 1 H, J = 3 Hz, acetylenic), and 2.45–1.25 ppm (m, 6 H, CH_2).

1-(Hex-5′-yn-1′-yl)-2-[(hydroxyimino)methyl]pyridinium Chloride (14). To 3.18 g (26.0 mmol) of 2-pyridine aldoxime in 125 mL of nitromethane at 0 °C was added 6.50 g (28.2 mmol) of 5-hexyn-1-yl trifluoromethanesulfonate over 10 min. The mixture was warmed to room temperature and stirred for 1 h. The solvent was evaporated in vacuo to a tan oil, which was ion-exchanged [Amberlite IRA-400 (Cl^-)]. The resulting solid was recrystallized from ethanol/ethyl acetate to afford 3.73 g of the title compound as a colorless solid: ^1H NMR (DMSO-d_6) δ 12.60 (s, 1 H, NOH), 9.40–8.05 (m, 4 H, aryl), 8.91 (s, 1 H, C*H*NOH), 4.91 (t, 2 H, J = 7 Hz, CH_2), 2.86 (t, 1 H, J = 3 Hz, CH), and 2.45–1.35 ppm (m, 6 H, CH_2).

Acknowledgment. This work was supported by U.S. Army Medical Research and Development Command Contract Nos. DAMD17-82-C-2194 and DAMD17-85-C-5154. We are indebted to Dorris Taylor and her staff of the Bioorganic Chemistry Laboratory, SRI International, for pK_a and log P measurements.

Registry No. **2a**, 117982-93-1; **2b**, 117983-05-8; **2c**, 117983-06-9; **2d**, 117983-07-0; **2e**, 117983-08-1; **2f**, 117983-09-2; **2g**, 117983-10-5; **2h**, 117983-11-6; **2i**, 117983-12-7; **2j**, 117983-13-8; **2k**, 117983-14-9; **2l**, 117983-15-0; **2m**, 117983-16-1; **2n**, 117983-17-2; **2o**, 117983-18-3; **3a**, 117982-94-2; **3b**, 117983-19-4; **3c**, 117983-20-7; **3d**, 117983-21-8; **3e**, 117983-22-9; **3f**, 117983-23-0; **3g**, 117983-24-1; **3h**, 117983-25-2; **3i**, 117983-26-3; **3j**, 117983-27-4; **3k**, 117983-28-5; **3l**, 117983-29-6; **3m**, 117983-30-9; **3n**, 117983-31-0; **3o**, 117983-32-1; **4a**, 91900-15-1; **4b**, 91900-17-3; **4c**, 117941-64-7; **4d**, 117983-33-2; **4e**, 117983-34-3; **4f**, 117983-35-4; **4g**, 117983-36-5; **4h**, 91900-16-2; **4i**, 117983-37-6; **4j**, 117983-38-7; **4k**, 117983-39-8; **4l**, 118017-01-9; **4m**, 117983-40-1; **4n**, 117983-41-2; **4o**, 117983-42-3; **4p**, 117983-43-4; **5**, 117982-95-3; **6**, 117982-96-4; **7**, 117982-97-5; **8**, 117982-98-6; **9**, 117982-99-7; **10**, 117983-00-3; **11**, 117983-01-4; **12**, 117983-02-5; **13**, 117983-03-6; **14**, 117983-04-7; 2-[(hydroxyimino)methyl]-1-methylimidazole allyl chloromethyl ether, 20062-62-8; chloromethyl 2-methyl-2-propen-1-yl ether, 58558-40-0; chloromethyl 2-methyl-3-buten-2-yl ether, 117983-44-5; chloromethyl 2(*E*)-buten-1-yl ether, 117983-45-6; 2(*Z*)-buten-1-yl chloromethyl ether, 117983-46-7; chloromethyl 2(*E*)-penten-1-yl ether, 117983-47-8; chloromethyl 2-(*Z*)-penten-1-yl ether, 117983-48-9; chloromethyl 2(*E*)-hexen-1-yl ether, 117983-49-0; chloromethyl 3-methyl-2-buten-1-yl ether, 117983-50-3; chloromethyl 4,4-dimethyl-2-penten-1-yl ether, 117983-51-4; chloromethyl 1-hexen-3-yl ether, 104620-71-5; 3-buten-1-yl chloromethyl ether, 117983-52-5; chloromethyl 3-hexen-1-yl ether, 117983-53-6; 4-[(chloromethyl)oxy]-2-methyl-1-butene, 117983-54-7; chloromethyl 2,5-dimethyl-1,5-hexadien-3-yl ether, 117983-55-8; chloromethyl 2-propyn-1-yl ether, 40308-66-5; 3-butyn-2-yl chloromethyl ether, 55812-23-2; chloromethyl 2-methyl-3-butyn-2-yl ether, 55812-22-1; chloromethyl 2-methyl-3-pentyn-2-yl ether, 117983-56-9; chloromethyl 3-pentyn-2-yl ether, 117983-57-0; chloromethyl 1-pentyn-3-yl ether, 117983-58-1; chloromethyl 1-hexyn-3-yl ether, 104620-72-6; 3-butyn-1-yl chloromethyl ether, 117983-59-2; chloromethyl 3-pentynyl ether, 117983-60-5; chloromethyl 4-pentyn-2-yl ether, 117983-61-6; *erythro*-chloromethyl 3-methyl-4-pentyn-2-yl ether, 117983-62-7; chloromethyl 1-heptyn-4-yl ether, 117983-63-8; chloromethyl 4-pentyn-1-yl ether, 117983-64-9; chloromethyl 2-ethynylcyclohex-1-yl ether, 117983-65-0; chloromethyl 1-ethynylcyclopent-1-yl ether, 117983-66-1; benzyl chloromethyl ether, 3587-60-8; chloromethyl 1-methylnaphthyl ether, 88045-68-5; chloromethyl (1,2,3,4-tetrahydronaphth-1-yl)methyl ether, 117941-72-7; chloromethyl 4′-(trifluoromethyl)benzyl ether, 117983-67-2; chloromethyl 4-fluorobenzyl ether, 104620-66-8; chloromethyl 2-[2′-(trifluoromethyl)phenyl]ethyl ether, 117983-68-3; chloromethyl 1-phenylbut-1-yl ether, 104620-67-9; chloromethyl 3-phenylpropyl ether, 90875-79-9; chloromethyl 4-phenylbut-1-yl ether, 117983-69-4; chloromethyl (cyclopentyl)-methyl ether, 104620-68-0; chloromethyl 3-phenylprop-2(*E*)-en-1-yl ether, 117983-70-7; chloromethyl 2-methyl-4-phenyl-3-butyn-2-yl ether, 117983-71-8; chloromethyl 1-phenyl-1-pentyn-3-yl ether, 117983-72-9; chloromethyl 4-methyl-1-phenyl-1-pentyn-3-yl ether, 117983-73-0; chloromethyl 1-phenyl-1-hexyn-4-yl ether, 117983-74-1; chloromethyl 1-phenyl-3-butyn-1-yl ether, 117983-75-2; 5-hexyn-1-yl trifluoromethanesulfonate, 85355-21-1; 4-hexyn-1-ol, 928-93-8; *tert*-butyl isothiocyanate, 590-42-1; aminoacetaldehyde diethyl acetal, 645-36-3; 1-*tert*-butyl-3-(2,2-diethoxyethyl)thiourea, 117983-76-3; 1-*tert*-butyl-2-mercaptoimidazole, 61640-27-5; *tert*-butylimidazole, 45676-04-8; 1-*tert*-butylimidazole-2-carboxaldehyde, 117983-77-4; 1-*tert*-butyl-2-[(hydroxyimino)methyl]-imidazole, 117983-78-5; hexynyl triflate, 85355-21-1; 3-*tert*-butyl-1-(hex-5′-yn-1-yl)-2[(hydroxyimino)methyl] imidazolium triflate, 117983-80-9; 1-(5′-hexynyl)imidazole-2-carboxaldehyde diethyl acetal, 117983-82-1; 1-(diethoxymethyl)imidazole, 61278-81-7; 1-(diethoxymethyl)-2-formylimidazole, 99651-38-4; 1,2-bis(diethoxymethyl)imidazole, 117983-81-0; 5-hexyn-1-yl methanesulfonate, 79496-61-0; 1-(hex-5′-yn-1′-yl)-2-[(hydroxyimino)methyl]imidazole, 117983-83-2; chloromethyl methyl ether, 107-30-2; buta-1,2-dien-4-yl chloromethyl ether, 117983-84-3; 1,2-dimethylimidazole, 1739-84-0; 3-[(hydroxyimino)methyl]-4-methyl-1,2,4-triazole, 117983-85-4; 1-(hex-5′-yn-1-yl)-3-[(hydroxyimino)methyl]-4-methyl-1,2,4-triazolium trifluoromethanesulfonate, 117983-87-6; 4-pyridine aldoxime, 696-54-8; 1-(hex-5′-yn-1′-yl)-4-[(hydroxyimino)methyl]pyridinium trifluoromethanesulfonate, 117983-89-8; 2-pyridine aldoxime, 873-69-8; 1-(hex-5′-yn-1′-yl)-2-[(hydroxyimino)methyl]pyridinium trifluoromethanesulfonate, 117983-91-2; acetylcholinesterase, 9000-81-1; atropine sulfate, 55-48-1.

Supplementary Material Available: Proton NMR spectral data for all new imidazolium compounds prepared in this study (Table A) (5 pages). Ordering information is given on any current masthead page.