fractions (~60 mL) were washed with 2 × 30 mL of 5% Na_2CO_3 solution, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. Purification by column chromatography afforded the azides on elution with hexanes.

***exo*-2-Azidobicyclo[2.2.1]heptane (2).** Treatment of 2-bicyclo[2.2.1]heptene (1) as outlined in Table I afforded azide 2 as a colorless liquid: IR 2960, 2090 ($-N_3$), 1450, 1245 cm^{-1}; ^1H NMR δ 3.45 (ddd, J = 7.6, 2.6, and 1.3 Hz, 1 H, CH-2n), 2.28 (m, 2 H, CH-1 and -4), 1.5 (m, 5 H), 1.1 (m, 3 H); ^{13}C NMR δ 64.0, 41.6, 37.8, 35.5, 34.9, 28.1, 25.5 (lit.[18] IR 2100 cm^{-1}; ^1H NMR (CCl_4) δ 3.55–3.25 (m, 1 H), 2.4–2.2 (m, 2 H), 1.7–0.95 (m, 8 H)).

1-Azido-1-methylcyclohexane (4). Treatment of 1-methylcyclohexene (3) as outlined in Table II afforded azide 4 as a colorless liquid: IR 2935, 2090 ($-N_3$), 1445, 1253, 1155 cm^{-1}; ^1H NMR (400 MHz) δ 1.68 (m, 2 H), 1.5 (m, 5 H), 1.40 (m, 2 H), 1.29 (s, 3 H), 1.25 (m, 1 H) (lit.[4] IR 2980, 2100, 1455, 1172 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5 (br s, 10 H), 1.3 (s, 3 H)).

***cis*- and *trans*-1-Azido-1,2-dimethylcyclohexane (*cis*- and *trans*-6).** Treatment of 1,2-dimethylcyclohexene (5) as outlined in Table II afforded a 1:1 mixture of azides *cis*- and *trans*-6. Anal. Calcd for $C_8H_{15}N_3$: C, 62.71; H, 9.87; N, 27.42. Found: C, 62.90; H, 9.80; N, 27.30.

Further purification by preparative HPLC on a silica column afforded, on elution with hexane, azide *cis*-6 as a colorless oil: IR 2920, 2085 ($-N_3$), 1465, 1255 cm^{-1}; ^1H NMR δ 1.60 (m, 9 H), 1.14 (s, 3 H, CH_3-1), 0.90 (d, J = 6.7 Hz, 3 H, CH_3-2); ^{13}C NMR δ 64.8, 39.2, 37.0, 31.0, 24.6, 22.9, 17.7, 15.9.[19]

Azide *trans*-6 was obtained as a colorless oil: IR 2940, 2090 ($-N_3$), 1455, 1255 cm^{-1}; ^1H NMR δ 1.87 (m, 1 H), 1.68 (m, 1 H), 1.53 (m, 2 H), 1.32 (m, 5 H), 1.31 (s, 3 H, CH_3-1), 0.89 (m, 3 H, CH_3-2); ^{13}C NMR δ 64.2, 40.9, 37.4, 30.7, 25.8, 24.7, 22.2, 15.8.[19]

1-Azido-2,3-dihydro-1*H*-indene (8). Treatment of indene (7) as outlined in Table II afforded azide 8 as a colorless liquid, which slowly decomposed at room temperature: IR 3070, 3020, 2940, 2090 ($-N_3$), 1475, 1455, 1230 cm^{-1}; ^1H NMR δ 7.4 (m, 1 H), 7.25 (m, 3 H), 4.85 (dd, J = 7.2 and 4.8 Hz, 1 H, CH-1α), 3.06 (ddd, J = 16.0, 8.2, and 6.6 Hz, 1 H, CH-3β), 2.85 (ddd, J = 16.0, 8.1, and 5.4 Hz, 1 H, CH-3α), 2.43 (dddd, J = 14.0, 8.1, 7.2, and 6.6 Hz, 1 H, CH-2α), 2.10 (dddd, J = 14.0, 8.2, 5.4, and 4.8 Hz, 1 H, CH-2β); ^{13}C NMR δ 143.3, 140.4, 128.5, 126.5, 124.7, 124.2, 65.6, 32.2, 30.1.

3-Azidocyclohexene (10). Treatment of 1,3-cyclohexadiene (9) as outlined in Table II afforded azide 10 as a colorless liquid, which slowly decomposed at room temperature: IR 3030, 2942, 2095 (N_3), 1651, 1451, 1256, 910, 735 cm^{-1}; ^1H NMR δ 5.97 (ddt, J = 1.5, 3.7, and 10.0 Hz, 1 H, CH-1), 5.67 (ddt, J = 2.2, 3.9, and 10.0 Hz, 1 H, CH-2), 3.82 (br m, 1 H, CH-3), 2.1 (m, 2 H), 1.72 (m, 4 H); ^{13}C NMR δ 132.7, 124.8, 55.9, 28.6, 24.7, 19.1 (lit.[20] ^1H NMR (CCl_4) δ 5.83 (m, 4 H), 4.0–3.6 (m, 1 H), 2.2–1.4 (m, 6 H)).

Studies on the Adsorption of CH_3SO_3H to Silica Gel and Alumina. To a solution of 65 μL (1.0 mmol) of CH_3SO_3H in 5 mL of $CDCl_3$ was added 2.5 g of SiO_2 that had been prepared as described above. Analysis by ^1H NMR of an aliquot removed after 5 min of stirring showed no detectable signal at δ 3.16 attributable to CH_3SO_3H. A similar experiment with Al_2O_3 using 2.0 mmol of CH_3SO_3H gave the same result.

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Registry No. 1, 498-66-8; 2, 22526-51-8; 3, 591-49-1; 4, 22530-83-2; 5, 1674-10-8; *cis*-6, 144192-65-4; *trans*-6, 144192-66-5; 7, 95-13-6; 8, 144192-67-6; 9, 592-57-4; 10, 16717-84-3; 11, 110-83-8; 12, 111-66-0; Al_2O_3, 1344-28-1; CF_3SO_3H, 1493-13-6; 4-$CH_3C_6H_4SO_3H$, 104-15-4; H_2SO_4, 7664-93-9; CH_3SO_3H, 75-75-2; $(CH_3)_3SiN_3$, 4648-54-8; HN, 7782-79-8.

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A Convenient Synthesis of Benzohydroximoyl Chlorides as Nitrile Oxide Precursors by HCl/*N*,*N*-Dimethylformamide/Oxone System

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Nitrile oxides are important intermediates in organic synthesis, particularly in [3 + 2] cycloaddition reactions to form isoxazolines or isoxazoles.[1] Among several methods developed for the in situ generation of nitrile oxides, two have been extensively used: (a) the dehydration of primary nitro derivatives (Mukaiyama procedure for aliphatic nitrile oxides)[2] and (b) the base-induced dehydrohalogenation of hydroximoyl chlorides (Huisgen's methodology for aromatic nitrile oxides).[3] Thus, convenient methods for the synthesis of substituted benzohydroximoyl chlorides (aromatic nitrile oxide precursors) have received much attention.[4] Previously reported preparations of benzohydroximoyl chlorides by chlorination of the corresponding aldoximes have required either the use of chlorine,[4a] nitrosyl chloride,[4b] and *tert*-butyl hypochlorite[4c] or a complex experimental procedure utilizing *N*-chlorosuccinimide (NCS) in *N*,*N*-dimethylformamide (DMF).[4d] While the NCS/DMF method provided satisfactory yields of products for several types of aromatic aldoximes, ring chlorination could not be controlled with the strongly activated aromatic aldoximes by electron-donating substituents. An alternative method for the chlorination of benzaldoximes having electron-donating substituents with *tert*-butyl hypochlorite in carbon tetrachloride suffered from low yields.

During our investigations on nitrile oxides,[5] we have found that anhydrous hydrogen chloride in DMF/Oxone (potassium peroxymonosulfate, Aldrich) system provides a particularly selective and by far the most convenient method of preparation of benzohydroximoyl chlorides 2 from the corresponding aldoximes 1 (Scheme I).

Isolated yields of products are excellent, and this method can be applied to benzaldoximes regardless the electronic nature of the substituents. Either *m*-CPBA or Oxone might be used[6] in the chlorination of benzaldoximes for the generation of Cl^+. However, the use of *m*-CPBA as an oxidant requires a tedious removal of *m*-chlorobenzoic acid from the product.

The reaction conditions and workup procedures for the preparation of benzohydroximoyl chlorides are very simple

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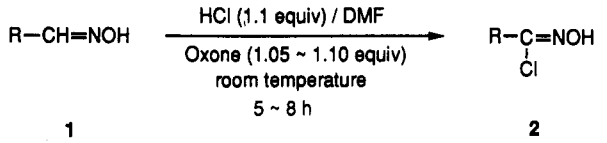
Scheme I



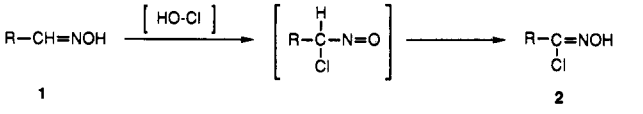
1 2

Table I. Preparation of Benzohydroximoyl Chlorides 2

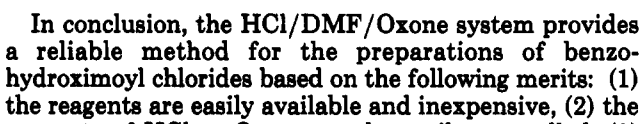
entry	R =	time (h)	yield[a] (%)	mp (°C) (lit. mp)
1	2-ClC_6H_4	8	95	56–58 (57–58)[7]
2	3-ClC_6H_4	8	99	65–67 (65–67)[4d]
3	4-ClC_6H_4	8	96	88–90 (87.5–89)[4d]
4	2,6-$Cl_2C_6H_3$	8	99	92–94 (93–94)[8]
5	3-$NO_2C_6H_4$	8	99	94–96 (94–96.5)[4d]
6	2-$CF_3C_6H_4$	8	99	81–82 (78–82)[4d]
7	4-$CF_3C_6H_4$	8	94	91–92 (89.5–91.5)[4d]
8	5-NO_2-2-furyl	8	80	143–145 (150)[9,b]
9	2-$CH_3OC_6H_4$	5	93	109–112 (112–112.5)[4d]
10	4-$CH_3OC_6H_4$	5	96	87–88 (87.5–88.5)[5]
11	3,4,5-$(CH_3O)_3C_6H_2$	5	91	128–130 (138–139)[4c,b]
12	2,4,6-$(CH_3)_3C_6H_2$	5	99	62–67 (61–69)[4d]
13	C_6H_5CO	8	94	130–132 (132–133)[10]
14	*tert*-butyl	5	92	oil (33)[11]

[a] Yields are of crude products which were pure by ^1H NMR and homogeneous by TLC. [b] Satisfactory elemental analysis (C, H, and N) was obtained.

and straightforward. Thus, a solution of benzaldoxime in 0.5 N anhydrous hydrogen chloride solution in DMF was treated with a slight excess of Oxone (1.05–1.10 equiv) at room temperature for 5–8 h. A small exotherm was noted. Cooling was more important in large-scale preparations. The reaction mixture was poured into cold water and extracted with ether to give products in the organic layers that were pure enough to be used directly in most cases. An excess (1.5–2.0 equiv) use of Oxone does not alter the yield or purity of products in the case of benzaldoximes having electron-withdrawing substituents but allows shortening of the reaction time. However, with a large excess of Oxone, benzaldoximes having electron-donating substituents give some ring chlorination. Thus, the use of only 1.05–1.10 equiv of Oxone is crucial here (entries 9–12). The present method can be applied to phenylglyoxaldoxime (2-isonitrosoacetophenone) as well as aliphatic aldoximes such as trimethylacetaldoxime. The results are summarized in Table I. A plausible mechanism for the chlorination of benzaldoximes is as follows: the hydrogen chloride is oxidized by Oxone to the positive chlorine species, hypochlorous acid. The reaction of the hypochlorous acid with the aldoximes 1 forms the nitroso intermediate,[4a] and this intermediate isomerizes to the hydroximoyl chlorides 2 as shown in eq 1.



(1)



1 2

In conclusion, the HCl/DMF/Oxone system provides a reliable method for the preparations of benzohydroximoyl chlorides based on the following merits: (1) the reagents are easily available and inexpensive, (2) the amounts of HCl or Oxone can be easily controlled, (3) initiation of the reaction and temperature control are not required, (4) workup procedures are convenient, and (5) regioselectively chlorinated pure products can be obtained in high yields.

Experimental Section

Melting points are uncorrected. All spectra were in accordance with the proposed structures.

Benzaldoximes were prepared according to the literature method from the corresponding aldehydes.[4c] Nifuroxime (*anti*-5-nitro-2-furaldoxime) and phenylglyoxaldoxime (2-isonitrosoacetophenone) were purchased from Aldrich and were used as received. Oxone was purchased from Aldrich. DMF was distilled from phosphorous pentoxide. Stock solution of anhydrous hydrogen chloride (0.5 N) in DMF was made by dissolving HCl gas in dry DMF.

General Procedure for the Synthesis of Benzohydroximoyl Chlorides 2. To a stirred solution of benzaldoxime (5 mmol) in a 0.5 N HCl stock solution in DMF (11 mL, 5.5 mmol of HCl) was added Oxone (1.62–1.69 g, 1.05–1.10 equiv of $KHSO_5$) at room temperature, and the reaction mixture was stirred at ambient temperature (a slight exotherm was noted) for 5–8 h. The reaction mixture was poured into cold water (100 mL) and extracted with ether (2 × 100 mL). The organic layers were washed with 0.5 N aqueous hydrochloric acid (100 mL) and brine (100 mL) and dried over anhydrous $MgSO_4$. Removal of ether gave the desired product. Analytically pure products were obtained by recrystallization from the reported solvents.[4c-d,5,7-11]

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Observations Concerning the Reactivity of Bicyclomycin and Bicyclomycin Derivatives with Organophosphorus Reagents

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Mechanistic proposals pertaining to the mode of action of the commercial antibiotic bicyclomycin[1,2] (1) have suggested that this agent alkylates the key protein(s) necessary for bacterial function.[3-6] To date chemical studies have demonstrated that the C(5)–C(5a) *exo*-methylene group in 1 is functionalized by sulfur[3,6] and nitrogen[7] nucleophiles under near neutral to basic conditions, while oxygen species[8] react at this site under acidic conditions. In this paper, we report the modification of the terminal double bond in bicyclomycin and 2[9-11] with

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